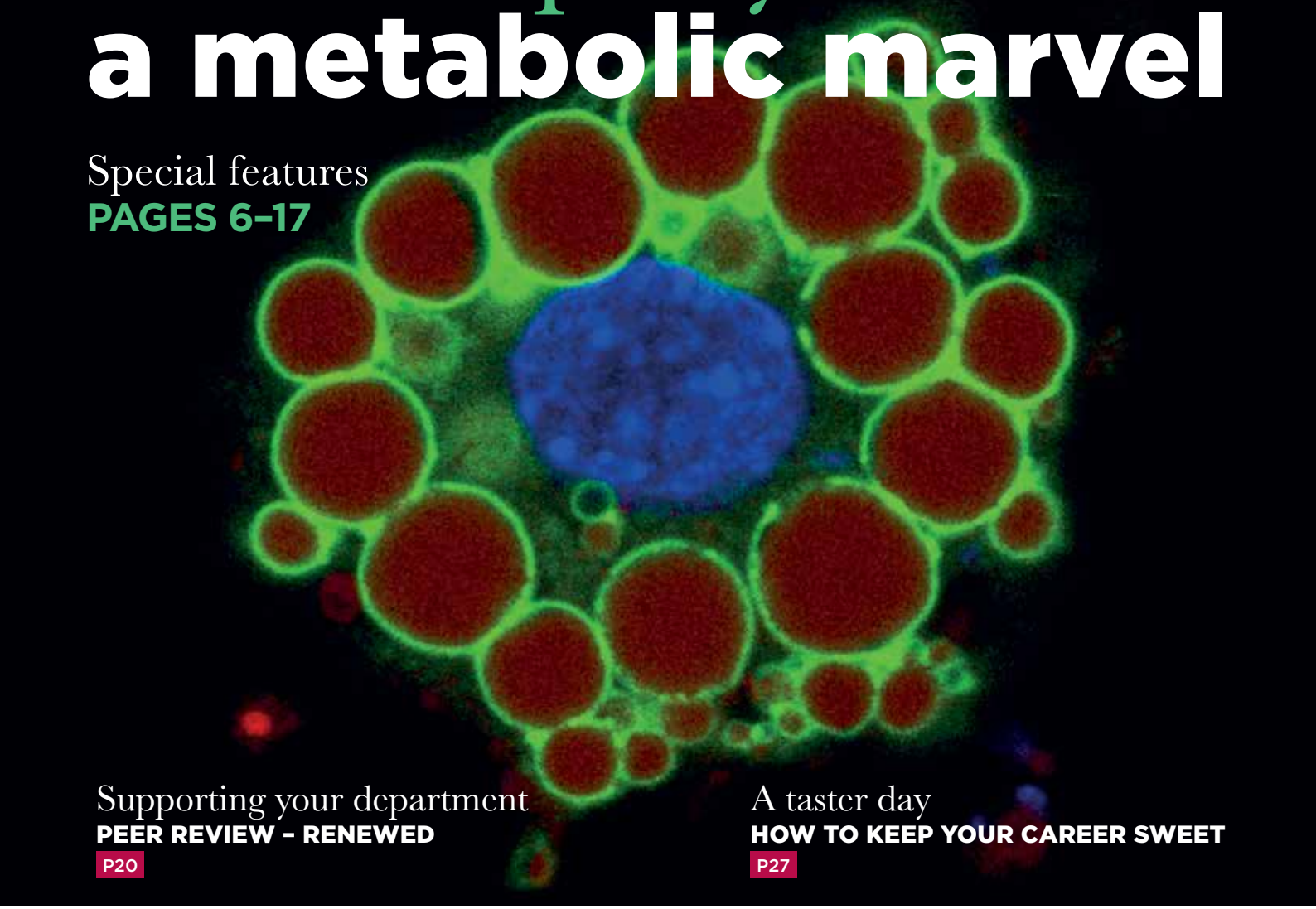
Society for Endocrinology

ISSUE 126 WINTER 2017
ISSN 0965-1128 (PRINT)
ISSN 2045-6808 (ONLINE)

THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

The adipocyte: a metabolic marvel



A word from THE EDITOR...

When I started at medical school, adipocytes were the 'magnolia woodchip' of the metabolic world. Beige but in a bad way: a boring, inert, storage cupboard that acted as a convenient filler to stop important organs jiggling together when we moved. Skip on a few decades and that world view seems risible. I am delighted that the once humble fat cell is the cover star of this edition, and that we have a cracking series of articles on all things adipose.

Justin Rochford starts off by bringing us up to speed on the basic biology of the fat cell, before Cannon and Nedergaard outline with great clarity the key physiological features of brown fat, and Mark Christian explores how adipocytes may be therapeutically modulated. Moving outside of these tissue depots, you can read a fascinating piece from Cawthorn and MacDougald on the role of fat in bone marrow, be reminded of the benefits of 'healthy fat' by Mann and Savage, and understand the spectrum of serious disorders that result from disorders of fat accumulation in the liver by Allison and Vacca. On top of all this, Paul Franks gives us an important insight into genetic precision as it applies to metabolism.

With a timely reminder from Antonia Brooke on the power of peer review, a very encouraging report on a career taster day and a 'tour de force' from Kevin Murphy, we round off the final issue of *The Endocrinologist* for this year.

This issue is also my final one as Editor. It's been a blast working on the magazine and I hope we as an Editorial Board have managed to maintain the very high standards of our predecessors. Huge thanks go to all at the Society for Endocrinology for offering endless support and giving us the freedom to go all over the place with ideas. A sincere thank you is offered to all who responded to my badgering emails and messages and delivered great articles again and again.

With the new team led by Amir, Helen and Eilidh, *The Endocrinologist* will be in safe hands and increasingly well positioned to take advantage of all that digital and social media have to offer. Now, more than ever, there is a need for clear, articulate comment and I know that the Society has within its membership some of the brightest and sharpest minds around. Please don't hold back in coming forward and contributing ideas, comments and articles.

Thanks for reading and thanks for getting involved.

TONY COLL

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Become a contributor... Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.
Deadline for news items for the Summer 2018 issue: **23 March 2018**.

Front cover image ©Satish Patel

We wish all our readers a very merry Christmas and happy new year

UPDATES AT *THE ENDOCRINOLOGIST*

The current Editor Tony Coll completes his term of office at the end of 2017. We are very grateful for his excellent work over the past 2 years. We look forward to working with Amir Sam as our new Editor , and Helen Simpson as our new Associate Editor from January 2018.

Kim Jonas also completes her term on the Editorial Board at the end of 2017, and we thank her for her great work on the magazine.

Amir Sam

Helen Simpson

HAVE YOU RENEWED YOUR MEMBERSHIP YET?

Don't let your membership lapse or you could miss out on great Society member benefits. Society member benefits are designed to help keep you at the forefront of endocrinology. A variety of funding and training opportunities are available, as well as discounts and free subscriptions for journals. Plus, new for 2018, members receive a 40% discount on Open Access publishing in *Endocrine Connections*.

Log in to the members' area now to renew online and visit **www.endocrinology.org/membership/member-benefits** to find out more.

EARLY CAREER PRIZE LECTURES 2018: CALL FOR ABSTRACTS

Abstracts are invited by 30 April from Clinicians-in-Training and Scientists-in-Training who wish to be considered for the Society's Early Career Prize Lectureships. The winners will receive a £750 honorarium, and will present their abstracts at the SfE BES 2018 conference on 19–21 November in Glasgow. Full details on submission are at **www.endocrinology.org/grants-and-awards/prizes-and-awards/early-career-prize-lectures**.

John Wass

JOHN WASS IS NEW GIRFT CLINICAL LEAD

Getting It Right First Time (GIRFT) is a national programme to improve medical care in the NHS by reducing unwarranted variations. We congratulate John Wass (Oxford), former President of the Society for Endocrinology, on his appointment as GIRFT Clinical Lead for Endocrinology. You can find out more at **www.gettingitrightfirsttime.co.uk/workstreams**.

SOCIETY UPDATES

We are pleased to announce that Professor Eleanor Davies (Glasgow) and Professor Duncan Bassett (London) will be the Society's next General Secretary and Programme Secretary. They will begin their terms of office at the next AGM.

Eleanor Davies

Duncan Bassett

WITH REGRET

We are very sorry to announce the deaths of Senior Members Dr Ron Fletcher and Professor John Ratcliffe.

BECOME A SOCIETY MEDIA AMBASSADOR

Share your expertise and help improve science and health reporting in the media. Media Ambassadors work alongside the Society's press office to provide accurate and responsible media reporting of endocrinology-related topics. Find out more in our free guide: **www.endocrinology.org/outreach/public-engagement/opportunities/engaging-with-the-media**

Catch up on the latest news and views via the Society for Endocrinology blog

THE ENDOCRINE POST: www.endocrinologyblog.org

SOCIETY CALENDAR

12 March 2018
SfE NATIONAL CLINICAL CASES MEETING
London

16–17 April 2018
ENDOCRINE NURSE UPDATE
Birmingham

16–18 April 2018
CAREER DEVELOPMENT WORKSHOP
Birmingham

16–18 April 2018
CLINICAL UPDATE
Birmingham

19–21 November 2018
SfE BES CONFERENCE
Glasgow

www.endocrinology.org/events for full details

SOCIETY SUPPORTED EVENTS

1 February 2018
OBESITY UPDATE
London, UK

27 February–2 March 2018
NUCLEAR RECEPTORS: NEW ROLES FOR NUCLEAR RECEPTORS IN DEVELOPMENT, HEALTH AND DISEASE
Cancun, Mexico

GRANT AND PRIZE DEADLINES

14 March 2018
SUMMER STUDENTSHIPS

28 March 2018
PUBLIC ENGAGEMENT GRANTS

11 April 2018
REGIONAL CLINICAL CASES MEETING GRANTS

25 April 2018
PRACTICAL SKILLS GRANTS

30 May 2018
THEMED SCIENTIFIC MEETING GRANT

www.endocrinology.org/grants for full details of all Society grants and prizes

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology, Journal of Molecular Endocrinology, Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, **www.endocrinology.org**. *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access (OA) and free to all.

JOURNAL OF ENDOCRINOLOGY

Role of oestrogen in skeletal response to leptin

Leptin is important for normal bone growth, maturation and turnover. Leptin-deficient (*ob/ob*) mice display osteopenia, reduced longitudinal bone growth and impaired cancellous bone maturation. However, leptin deficiency also results in gonadal dysfunction, disrupting hormones which in turn regulate bone growth and turnover.

In order to unpick these processes, Turner *et al.* measured bone parameters in *ob/ob* mice receiving vehicle, leptin and leptin plus an oestrogen receptor antagonist. Mice in the last group did not differ in bone formation rate but had higher longitudinal bone growth rate and cancellous bone volume fraction compared with those receiving leptin alone.

The authors conclude that increased oestrogen signalling following leptin treatment is not necessary for the positive actions on bone, and may attenuate leptin-induced bone growth.

Read the full article in *Journal of Endocrinology* **233** 357–367

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Stem cell-derived exosomes in tissue repair and diabetic therapy

The secretion of extracellular vesicles from cells into the extracellular environment is increasingly recognised as an important modality for mediating cell–cell communication. Extracellular vesicles are secreted from most cell types and carry biological macromolecules, including RNA, lipids and proteins. The composition of extracellular vesicles changes in physiological and pathological conditions, and roles have been described in repair and regeneration. Thus, there is high interest in deciphering the functional roles of extracellular vesicles, and their potential for therapeutic use.

In this review article, Newton *et al.* discuss the role of stem cell-derived exosomes in tissue repair and regeneration, and their potential use for the treatment of type 1 diabetes mellitus.

Read the full article in *Journal of Molecular Endocrinology* doi:10.1530/JME-17-0080

ENDOCRINE-RELATED CANCER

The future of MEN1 therapy and management

Management of pancreatic neuroendocrine tumours (P-NETs) remains a challenge in multiple endocrine neoplasia type 1 (MEN1). Sadowski *et al.* have provided an excellent overview of the literature, which helps decision-making in this field.

One take home message for me was that P-NETs <2cm and stable can be observed. Endoscopic ultrasound has a better pick-up rate than magnetic resonance imaging (MRI) for P-NETs. If seen on both modalities, MRI can be used for surveillance every 1–3 years. Liver MRI remains the best imaging modality for detecting liver metastases and there is no evidence to support use of Gallium-68 positron emission tomography in surveillance strategies. We need to be mindful of long term surveillance strategies and radiation dosing, and increasing anxiety, particularly in young patients.

In terms of surgery, all seem to agree that total pancreatectomy is not advisable. Whilst some advocate aggressive procedures such as distal pancreatectomy, head of pancreas enucleation and duodenectomy, there has been high risk of complications. Most surgeons favour a more conservative approach, accepting that repeat surgery may be necessary.

Again, the French seem to lead the field with national registries. Without nationwide long term observational clinical data, we will not understand which interventions work and improve outcomes for our patients.

Read the full article in *Endocrine-Related Cancer* **24** T243–T260

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

Maternal exercise improves glucose tolerance in female offspring

Studies in humans and animals have highlighted that offspring exposed to maternal obesity are themselves at risk of obesity and type 2 diabetes in later life. In rodents, maternal exercise has been shown to have beneficial effects on the metabolic phenotype of adult male offspring.

Since males and females are differentially affected by numerous metabolic insults and disease states, Standford and colleagues investigated the effects of maternal exercise in the presence of a maternal high fat diet on female offspring. They found that the detrimental effects of a maternal high fat diet on glucose tolerance in female offspring were ablated by maternal exercise that was carried out both before and during pregnancy. This was also accompanied by improved liver function in these offspring.

One important implication of the improvement of metabolic health in female offspring of exercised high fat fed dams is that this intervention could potentially halt the intergenerational transmission of obesity and diabetes.

Read the full article in *Diabetes* **66** 2124–2136

Hot Topics is written by Navpreet Chhina, Kim Jonas, Eilidh McGregor, Edouard Mills, Lisa Nicholas, Rozana Ramli and Helen Simpson.

CLINICAL ENDOCRINOLOGY

Phaeochromocytoma in MEN2: *RET* codon-specific penetrance

Multiple endocrine neoplasia type 2 (MEN2) is characterised by tumour development in various endocrine organs and is caused by germline missense mutations in the *RET* proto-oncogene.

In a retrospective study conducted in a specialised ambulatory care centre in Germany, Mucha *et al.* aimed to characterise the exon- and codon-specific penetrance and age-related development of phaeochromocytoma among 309 MEN2 patients. Phaeochromocytoma penetrance and age of diagnosis were highly correlated with medullary thyroid cancer (MTC) aggressiveness based on *RET* mutation status, with higher penetrance and younger age of diagnosis associated with more aggressive MTC. Penetrance steadily increased with age.

The authors comment that while *RET* mutations at codon 634 and 918 are reported to be strongly associated with the presence of phaeochromocytoma, it is still necessary to screen the MEN2 kindred for phaeochromocytoma, regardless of the *RET* mutation present. At-risk patients require lifelong follow-up.

Read the full article in *Clinical Endocrinology* **87** 320–326

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Acute Cushing's in an HIV-infected child on antiretrovirals

Dubrocq *et al.* describe an 11-year-old child who was being treated for perinatally acquired HIV with multiple agents: abacavir plus lamivudine (Epzicom), didanosine and ritonavir. Two months after an intra-articular injection of triamcinolone, he had symptoms of fatigue and a Cushingoid appearance. Investigations demonstrated an undetectable urinary free cortisol together with a flat synacthen test, confirming hypothalamo-pituitary-adrenal axis suppression.

Whilst not a new finding, this highlights drug–drug interactions with antiretrovirals. Although triamcinolone has a half-life of 3h, an intra-articular injection may be systematically absorbed for 3 weeks after injection, and adrenal suppression may last as long as 30 days. Co-administration of ritonavir and glucocorticoids may result in an increase in plasma corticosteroid levels, as they are both eliminated by CYP3A metabolism, and this interaction prolongs the half-life of triamcinolone several-fold. If a patient is on glucocorticoids, the antiretroviral regimen can be changed by replacing ritonavir with a non-protease inhibitor-based regimen to prevent this. The excellent website **www.hiv-druginteractions.org** lists drug interactions.

This case also emphasises the importance of taking a detailed history of glucocorticoid administration and highlights the need to manage patients safely. Whilst patients may have evidence of glucocorticoid excess they may also need stress dosing of hydrocortisone for surgery, intercurrent illness etc.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* **10** EDM170076

ENDOCRINE CONNECTIONS

Preferential amyloid deposit formation in the most blood-perfused islets

Aggregates of islet amyloid polypeptide (IAPP), which are cytotoxic, occur in type 2 diabetes. These lesions are heterogeneous, leading to inconsistencies in β-cell death between islets or between different parts of the pancreas. This is in line with the heterogeneous nature of pancreatic islets including differences in blood supply, which the authors previously described; low blood supply results in islets with dormant metabolic activity, whilst islets with increased blood supply exhibit raised glucose-stimulated insulin secretion.

Since IAPP is co-secreted with insulin, and increased IAPP production and secretion trigger aggregate formation, Ullsten *et al.* sought to determine whether a subpopulation of highly perfused islets would be more predisposed to amyloid formation. They used human IAPP-expressing mice fed a high fat diet and adopted a microsphere technique to identify highly blood-perfused, highly functional islets. The authors found preferential amyloid development in these islets, along with 30% higher glucose-stimulated insulin secretion.

These findings suggest that, although islets can increase insulin secretion to compensate for raised insulin resistance, this may inadvertently lead to increased amyloid aggregates in these islets, thus accelerating the progression of type 2 diabetes.

Read the full article in *Endocrine Connections* **6** 458–468

Percutaneous coronary intervention in stable angina (ORBITA): why all the fuss?

As a non-cardiologist, it has been interesting to observe the debate around the ORBITA study. Al-Lamee *et al.* conducted a well designed multicentre double blind trial of percutaneous coronary intervention (PCI) versus a placebo procedure for angina relief. Patients had severe single vessel disease with exertional symptoms. They were started on medication, then after 6 weeks randomised to PCI (105 patients) or placebo/sham procedure (95 patients).

No difference in the primary end-point, exercise time increment to symptoms, was noted after 6 weeks, suggesting drug treatment should be maximised in the management of stable angina, potentially denying a generation of interventional cardiologists a procedure to perform.

As you might imagine, much debate (see #ORBITA for highlights) and some detailed reviews of the paper and statistics have ensued. The study shows that placebo procedures are possible and trials can be designed in the same way as for pharmacological interventions. Some have suggested the study was underpowered to see a small number of differences in outcomes in this time period. However, the data seem to suggest drug therapy should be maximised first in stable angina, before implementing PCI with its known risks. These are quoted as a death rate of 0.65%, myocardial infarction (15%) and renal injury (13%). But what do I know? I'm a simple endocrinologist.

Read the full article in *The Lancet* doi:10.1016/S0140-6736(17)32714-9

Hormonal contraception and increased risk of depression

Recent findings indicate an increased risk for suicide attempt and suicide among women who use hormonal contraception.

Skovlund *et al.* carried out a nationwide prospective cohort study of all women in Denmark with no psychiatric diagnoses, antidepressant use or hormonal contraceptive use before age 15 years, who turned 15 between 1996 and 2013. Hormonal contraception, suicide attempt, suicide and potential confounding variables were determined via nationwide registers.

Among nearly half a million women followed on average for 8.3 years, there were 6,999 first suicide attempts and 71 suicides. Use of hormonal contraception was positively associated with subsequent suicide attempt and suicide, with adolescent women experiencing the highest relative risk. The association between hormonal contraceptive use and a first suicide attempt peaked after 2 months of use.

Read the full article in *American Journal of Psychiatry* doi:10.1176/appi.ajp.2017.17060616

ADIPOSE TISSUE: A FAT LOT OF GOOD?

WRITTEN BY JUSTIN ROCHFORD

Fat may be one of the most under-appreciated tissues in the body. It comprises lipid-laden mature adipocytes and precursor stem cells, along with other specialised cell types, all entwined in a network of extracellular matrix, blood vessels and nerves. Hence, adipose tissue is not the lump of inert blubber it may seem. Indeed, the critical roles adipose tissue plays in human health are still frequently overlooked. Instead, it can be disregarded as an irrelevance, a cosmetic imperfection or assumed to be 'a bad thing', when in fact it is (or should be) performing an array of remarkable and complex functions.

ADIPOCYTES AS EXPANDABLE STORAGE

The importance of appropriately functioning adipose tissue is most clearly illustrated by rare individuals suffering from a generalised lack of fat, or lipodystrophy, which leads to multiple endocrine and metabolic problems.

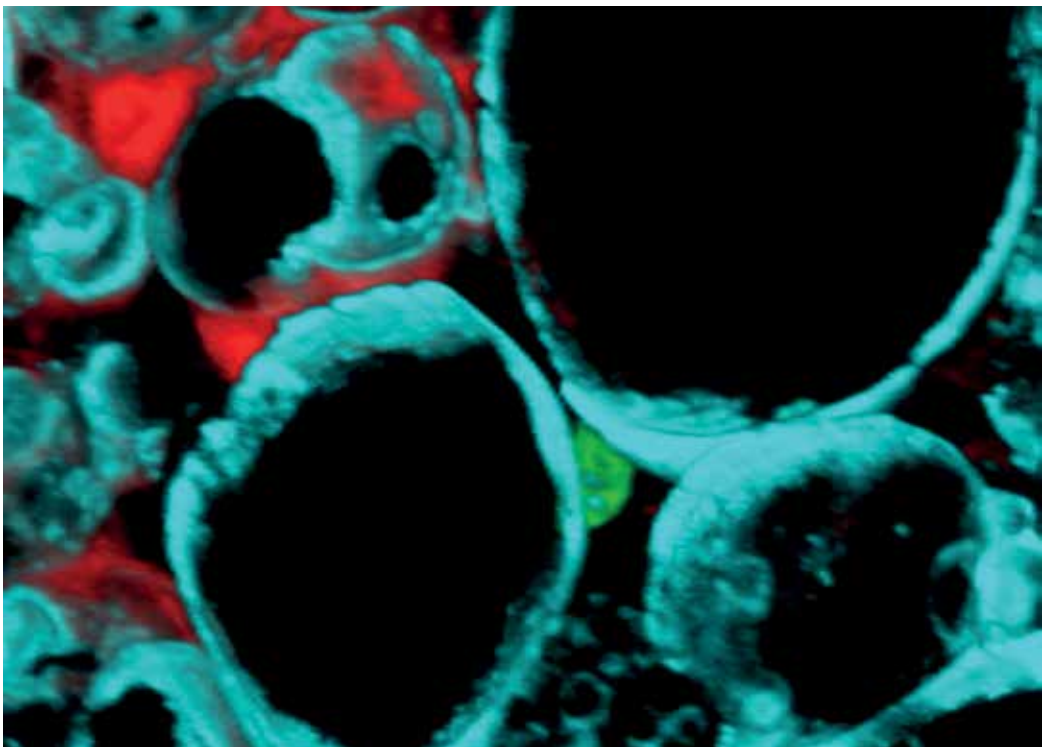
Counterintuitively, the mechanisms underlying these problems are likely to be shared in obese individuals. This was probably first articulated by RD Lawrence as long ago as 1946.[1] Describing a patient with lipodystrophy, fatty liver and diabetes, he noted that 'No fat could be stored in the usual depots, and so it circulated in excess and produced lipaemia.' He went on to discuss diabetes in obesity, hypothesising that this arises from 'such an overfilling of the fat depots that they can no longer accept and absorb an excess of sugar from food.' As such, he elegantly identified that the lack of available storage capacity is a mechanism by which a lack of fat development or the over-expansion of adipose tissue can cause similar health problems.

Hence the first, and almost certainly the most critical, job of adipose tissue is to act as a safe store for lipids. Losing this capacity leads to inappropriate lipid accumulation and dysfunction in other tissues.

Adipose tissue also provides a readily mobilised source of energy when required. This requires a complex co-ordinated response to endocrine and neuronal signals to precisely regulate nutrient uptake, processing, storage, breakdown and release.[2] The typical white adipocyte can measure over 0.1mm in diameter. Occupying at least 90% of its volume is a single, huge droplet of lipid. Everything else this cell must do is achieved in a thin, surrounding 'skin' of cytoplasm. Given the range of its abilities this is a remarkable feat.

One of the other key roles of the adipocyte is to secrete local and systemically acting endocrine factors.[3] Probably best known of these are the centrally acting satiety factor leptin, and the protein adiponectin, whose levels are closely correlated with insulin sensitivity. However, many others have been described with a bewildering array of effects, some beneficial and others harmful to the metabolic health of the individual. In addition to these roles, adipose tissue can act as a mechanical barrier against injury and provide insulation from the cold.

3D rendering of a 100-µm thick section of murine adipose tissue in the kidney. Immunofluorescent staining for the lipid droplet protein perilipin is in cyan. A lineage tracing Cre-induced tdTomato fluorescent protein labels a subset of adipocytes red. In the centre, the nucleus of a resident adipose stem cell is labelled green. ©J. Rochford



LOCATION, LOCATION, LOCATION

Where fat accumulates in the body can have significantly different effects on health. Subcutaneous white adipose tissue is generally beneficial, whilst expansion of visceral white adipose tissue in obesity is strongly correlated with metabolic disease. However, this broad statement hides the fact that different adipose depots are highly specialised and varied in function.

For example, unlike other fat, bone marrow adipose tissue increases during calorie restriction.[4] Indeed, bone marrow fat can be subdivided into at least two anatomically and functionally distinct types. Several depots of thermogenic brown adipose tissue exist, as well as cells that share some features of both white and brown adipocytes (so-called brite or beige adipocytes). Their presence in adult humans has led to intense interest in harnessing their ability to 'burn' stored lipids then dissipate the energy, as an

'The first, and almost certainly the most critical, job of adipose tissue is to act as a safe store for lipids.'

anti-obesity therapy.[5] Overall, targeting the development or function of defined adipose types could favour metabolically healthy fat tissue, with the potential to significantly improve health in obesity.

UNDER-EXPLORED DEPOTS: FAT IN FUNNY PLACES

As well as systemic effects, adipose tissues may also more specifically influence closely associated tissues. Perivascular adipose tissue can locally affect vascular function. Adipose tissue in the joints plays key roles in their maintenance, with changes in its function contributing to joint disorders such as osteoarthritis. Small depots of adipocytes exist within or adjacent to the heart, kidney, eyes and elsewhere. Teasing apart what each one does in its specific location is likely to reveal new insights regarding adipocyte function that have been missed by more generic analyses of well-studied adipose depots.

The adipocytes that comprise different depots can develop from several distinct populations of stem cells, whose nature can dictate the overall function of the tissues they generate.[6] Understanding their identity and potential has importance beyond the function of fat, as stem cells isolated from adipose tissue have been used therapeutically to generate a variety of cell types.

Such is the complexity of the origins and functions of adipocytes between and within different depots. Some are dedicated to long term storage, some provide an on-site fuel source, whilst others are releasing endocrine signals or generating heat. The range of abilities is remarkable. Not bad for the humble fat cell.

JUSTIN ROCHFORD
Reader in Metabolic Health, Rowett Institute, University of Aberdeen, UK

REFERENCES

1. Lawrence RD 1946 *Lancet* **247** 773–775.
2. Morigny P *et al.* 2016 *Biochimie* **125** 259–266.
3. Choi CHJ & Cohen P 2017 *Experimental Cell Research* doi:10.1016/j.yexcr.2017.04.022.
4. Scheller EL *et al.* 2016 *Trends in Endocrinology and Metabolism* **27** 392–403.
5. Kajimura S *et al.* 2015 *Cell Metabolism* **22** 546–559.
6. Sanchez-Gurmaches J & Guertin DA 2014 *Biochimica et Biophysica Acta* **1842** 340–351.

BROWN (AND BROWN-LIKE) ADIPOCYTES: THEIR ROLE AND POTENTIAL

WRITTEN BY BARBARA CANNON AND JAN NEDERGAARD

As human beings, we have a virtually constant body temperature. This is absolutely essential for our survival. The same is true for all mammals. We all know how unpleasant it is to stand waiting for a bus on a miserable November morning with wind and rain beating down on us. We start to shiver: this increases our metabolism and thus generates heat to defend our body temperatures. However, shivering is very uncomfortable and can only be maintained for a short time.

Fortuitously, if we are exposed to such cold conditions for a prolonged time, we instead start to develop a remarkable new ability, an alternative to shivering: the ability to generate heat by comfortable non-shivering means.

This comfortable heat generation occurs in brown adipocytes, cells filled with specialised mitochondria. These mitochondria can convert energy from our food directly into heat, without needing to first synthesise and then degrade ATP. They have acquired this unique ability because of the presence in the mitochondrial membranes of a protein termed uncoupling protein 1 (UCP1).

TRIGGERING THE RELEASE OF HEAT

When our body temperature is threatened, areas in the brain will be activated, located in the hypothalamus. From these areas, signals are sent down the spinal cord and ultimately to nerves that innervate the brown adipocytes in the brown adipose tissue depots. These nerves are part of the sympathetic nervous system and their stimulation leads to the release of norepinephrine in the tissue.

We seldom allow ourselves to feel uncomfortably cold, but rather stay in warm rooms or put on extra clothing; we thus live under thermoneutral conditions. Because of this, the thermogenic capacity of the brown adipocytes is normally very limited. Nonetheless, the small heat-producing

capacity that we have is activated by the sympathetic signal. The norepinephrine binds to β_3-adrenergic receptors on the mature brown adipocytes, and heat is produced.

Since the capacity is initially inadequate to meet the demands of a cold stress, the sympathetic signal also interacts with stem cells in the tissue that start to proliferate and subsequently to differentiate into fully mature new brown adipocytes. This thus increases the capacity of the tissue for heat production, and the need for the uncomfortable shivering consequently diminishes.

SOURCING FUEL

To produce heat, it is necessary to have something to burn. The brown adipocytes contain stored triglycerides in numerous small lipid droplets. This fat is what is initially used for heat production: the fatty acids generated by lipolysis of the fat droplets are delivered to the mitochondria.

However, this supply is limited, and it is necessary to import additional substrates from the circulation. These can be in the form of fatty acids or glucose, both of which are readily taken up and combusted by the brown adipocytes.

A ROLE IN COMBATTING OBESITY?

Since the process of heat production in brown adipose tissue thus combusts substrates, it can be envisaged that it could combust excess food that we consume. This process was suggested as long ago as 1979 to have a significant effect on regulation of body weight. Tasty diets were served to animals, and the more brown adipose tissue the animals had, the less weight they gained on the tasty diets. Remarkably they obtained more brown adipose tissue merely through eating these diets.

Although this observation created considerable interest at the time, it was nonetheless thought not to be readily applicable to adult humans, since it was believed that brown adipose tissue in humans disappeared in the first years of life. However, about 10 years ago, positron emission tomography (PET) scans of adult human patients indicated that brown adipose tissue was indeed present in many adult humans.

'Since the process of heat production in brown adipose tissue thus combusts substrates, it can be envisaged that it could combust excess food that we consume. This process was suggested as long ago as 1979 to have a significant effect on regulation of body weight.'

Most adult humans probably have some brown adipose tissue until they reach their 40s or 50s. The depots of identifiable brown adipose tissue are fairly small and their contribution to whole body metabolism has not yet been adequately determined. It seems perhaps unlikely that the physiological capacity would be such that it could treat human obesity. A more attractive possibility would be to be able to keep the brown adipocytes active for the whole life course, which could potentially reduce the development of 'middle-aged spread'.

DISCOVERIES IN WHITE ADIPOSE TISSUE

In addition to the brown adipocytes found in the classical brown adipose tissue depots in mice, there are adipocytes within classical *white* adipose tissue depots that have the ability to express UCP1 and potentially become heat-generating and energy-consuming. These cells are termed brite (brown-in-white) or beige or recruitable, and the process of their development is termed 'browning'.

In mice, in addition to enhanced sympathetic drive, numerous compounds and treatments have been shown to induce browning. In many cases, this is associated with a less marked development of body weight in animals fed a high fat, high sugar diet. To what extent it is the browning process and not acquiring more real brown adipocytes that actually leads to weight regulation is not really clear. Even more debatable is whether this browning of white adipocytes is valid in humans.

'It will be of considerable interest to evaluate to what extent the brown adipocytes may influence human metabolism and physiology, not only through their thermogenic and energy-expending properties, but also by functioning as an endocrine and paracrine organ.'

There are two aspects here. One is the nature of the brown adipose tissue present in humans. It has been claimed that the human tissue is more similar to the rodent brite/beige adipose tissue, but this has also been said not to be the case. This may be of importance, since the different UCP1-containing adipose tissue depots have different cellular origins, and the cells may therefore be responsive to different stimulatory agents. This could influence the development of relevant therapeutic agents to both activate existing UCP1-containing cells and to recruit new such cells. The other issue is whether adult humans do, in fact, have a significant set of recruitable UCP1-containing adipocytes in their classical white adipose depots. This is as yet unclear.

THE ADIPOCYTE SECRETOME

A further aspect of adipose tissue metabolism that has attracted interest recently is the so-called secretome, that is to say the array of molecules that are secreted from adipocytes under different circumstances.

For white adipocytes, the most well known is the hormone leptin, though dozens more are also secreted. The studies are still on-going in brown adipocytes. It will be of considerable interest to evaluate to what extent the brown adipocytes may influence human metabolism and physiology, not only through their thermogenic and energy-expending properties, but also by functioning as an endocrine and paracrine organ.

BARBARA CANNON & JAN NEDERGAARD
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WHY ARE OUR BONES FULL OF FAT? THE SECRETS OF BONE MARROW ADIPOSE TISSUE

WRITTEN BY WILLIAM P CAWTHORN & ORMOND A MACDOUGALD

Stop and think about your bones: what images come to mind? Perhaps a skull with grinning jaws, or the strong white limbs stretching out towards your fingers and toes. You might even think of the bone marrow within them, producing the blood that courses through your veins. But this is not the whole picture, for your skeleton hides a secret: it is full of fat, and no one knows why.

AN UNSOLVED MYSTERY

This unsolved mystery is surprising. Scientists first noticed that our bone marrow contains fat-storing cells, called adipocytes, over a century ago.[1] Having adipocytes in our bones might strike you as unusual, but it is not: in mammals, bone marrow adipose tissue (MAT) develops steadily after birth and accumulates rapidly during puberty such that, by the time we reach adulthood, it can comprise up to 70% of bone marrow volume – this represents over 8% of total fat mass![2]

MAT is not distributed uniformly around the skeleton, but instead predominates in the arms and legs. This peripheral MAT develops early after birth and is rarely depleted, and thus has been termed 'constitutive MAT' (cMAT).[3] In contrast, more central sites, such as the spine, pelvis and sternum, as well as more proximal regions of the long bones, contain less MAT and more haematopoietic red marrow (see Figure). At these sites, marrow adipocytes are more diffuse and tend to increase or decrease in response to environmental or pathological factors; hence, this depot has been dubbed 'regulated MAT' (rMAT).[3]

Other properties of marrow adipocytes also vary across these skeletal sites, with potential implications for the impact of MAT on health and disease.[2,3] Indeed, MAT further increases with ageing and in diverse clinical conditions, including skeletal, metabolic and haematological diseases (Figure). Consequently, MAT is now attracting considerable interest as a potential player in the development of numerous diseases. However, unlike white and brown adipose tissues (WAT and BAT respectively), the study of MAT has been relatively limited. Consequently, the physiological and pathological functions of MAT remain poorly understood.[4] So, what is the function of MAT, and how might it affect human health?

BAD TO THE BONE?

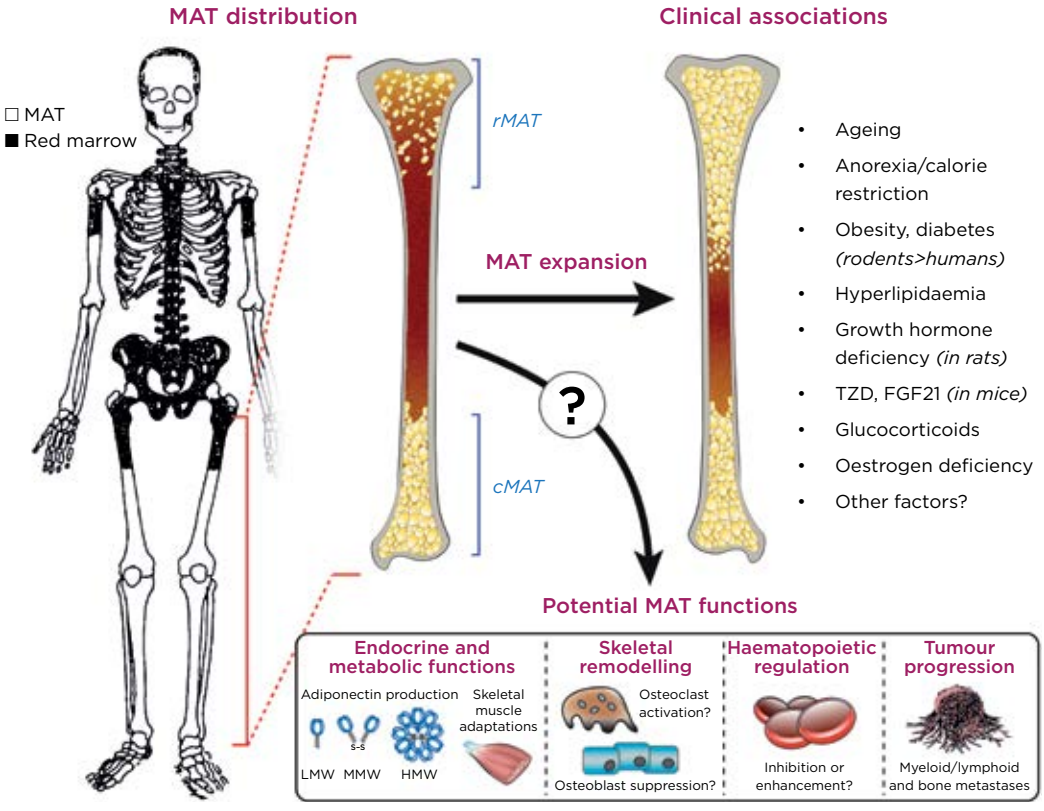
Increased bone marrow adiposity (BMA) is associated with lower bone mineral density and increased skeletal fragility, for example in osteoporosis, ageing and oestrogen deficiency.[5] This has motivated research into how MAT has an impact upon skeletal integrity.

One possibility is that bone marrow adipocytes share the same skeletal stem cell precursor as bone-forming osteoblasts, in which case MAT accumulation might occur at the expense of osteoblast development.[6] However, whilst this is true during embryonic development, it isn't firmly established if this common precursor persists through to adulthood to contribute to postnatal tissue maintenance.

Another possibility is that bone marrow adipocytes secrete local factors that directly impair bone formation and/or stimulate bone resorption, thereby increasing fracture risk.[7] Intriguingly, such paracrine actions might also promote the growth of tumours within the bone, whether primary myeloid/lymphoid cancers, or metastases from elsewhere (Figure).[8,9]

Is MAT accumulation therefore bad for bone health? Unfortunately, it is too early to tell. Although increased MAT may be associated with elevated fracture risk, increased MAT is not always associated with bone loss. The potential impact of MAT on skeletal tumour development

The anatomical distribution, clinical associations and potential functions of bone marrow adipose tissue (MAT). The image of the skeleton is adapted from Kricun (1985)[16]. cMAT, constitutive MAT; rMAT, regulated MAT; TZD, thiazolidinediones; FGF21, fibroblast growth factor 21; LMW/MMW/HMW, low/medium/high molecular weight.



also remains to be fully understood. Given the public health challenges posed by osteoporosis, skeletal cancers and ageing-associated diseases, elucidating these functions of MAT is a major goal of ongoing research.

HAEMATOLOGY

The key function of bone marrow is in blood cell production, so it is unsurprising that many of the earliest studies of MAT were pursued from a haematological perspective. Generally, decreased BMA is associated with increased haematopoiesis,[10] suggesting a suppressive effect of MAT.

Supporting this possibility, a landmark 2009 paper revealed that blocking MAT accumulation enhances haematopoietic recovery after bone marrow transplantation.[11] This has important translational implications: many recipients of bone marrow transplants show poor long-term recovery, and therefore suppressing marrow adipogenesis might represent a novel therapeutic approach.

However, not all data support a negative effect on haematopoiesis. Indeed, recent research suggests that, in the context of bone marrow transplants, marrow adipocytes secrete a molecule called stem cell factor, through which they promote haematopoiesis and the regeneration of haematopoietic stem cells.[12] Thus, as for the putative effects of MAT on bone, its impact on haematopoiesis is proving to be more complex than first suspected (Figure).

BEYOND THE BONE: METABOLIC AND ENDOCRINE FUNCTIONS

Although MAT's functions within the bone and marrow remain to be conclusively established, it seems clear that marrow adipocytes can influence skeletal homeostasis and haematopoiesis by secreting locally acting factors. But does MAT, like WAT, also secrete endocrine products to exert systemic metabolic effects?

Recent studies from our labs and others support this possibility. Numerous reports show that bone marrow adipocytes produce leptin, the prototypical adipocyte-derived hormone that has a major influence over energy homeostasis, inflammation and reproductive function.[7] We have found that, as in WAT, leptin expression in MAT is suppressed in response to decreased caloric intake,[13] demonstrating that MAT and WAT share common mechanisms to regulate their endocrine functions.

Whether MAT contributes to circulating leptin remains unknown, but its function as a source of other endocrine factors is becoming clear. A major focus of our research has been on MAT as a source of adiponectin, the other major hormone produced by adipose tissue. Despite this adipose source, circulating adiponectin is decreased in obesity and increased in states of leanness, such as during caloric restriction. Even after 20 years of extensive research on adiponectin, the basis for this so-called 'adiponectin paradox' had remained incompletely understood; why would an adipose-derived hormone be increased when WAT is lacking?

It was through this lens that we began to view MAT in a new light. In stark contrast to WAT, MAT formation increases in starvation states, such as during caloric restriction in animals and in human patients with anorexia nervosa.[14] Both MAT and circulating adiponectin are also increased in many other conditions, such as ageing, oestrogen deficiency and following treatment with glucocorticoids or anti-diabetic drugs (Figure).[4] But are these mere coincidences, or does MAT actually contribute to circulating adiponectin?

To answer this question, we combined clinical observations with studies in a unique mouse model that resists MAT formation. These approaches revealed that, during caloric restriction, MAT expansion is required for the full increases in circulating adiponectin,[15] a conclusion since supported by our more recent research.[4,13] MAT expansion during caloric restriction also appears to influence metabolic adaptations within skeletal muscle.[15] It is unclear if this is via adiponectin or other endocrine factors, but it underscores the potential of MAT to exert systemic effects.

FUTURE MATTERS

Over the past decade, the burgeoning field of MAT research has hugely advanced our understanding of MAT formation and function. MAT is no longer considered an inert 'space filler' within the bone marrow, but an active tissue with diverse implications for skeletal remodelling, tumour progression, haematopoietic regulation, and systemic endocrine and metabolic functions. Nevertheless, the study of MAT still falls far behind that of WAT and BAT, and therefore many key questions remain to be firmly answered.

Thankfully, a broad scientific community is now coalescing around MAT research. The first international meeting on BMA was held in Lille, France, in 2015, with successful follow-up meetings in 2016 and 2017. At the 2017 BMA meeting in Lausanne, Switzerland, attendees voted to establish the International Bone Marrow Adiposity Society, which aims to advance knowledge of BMA (**www.bma-society.org**). These developments highlight the increasing interest and enthusiasm for study of MAT. Therefore, we can be confident that future research efforts will continue to unlock fundamental knowledge of MAT biology, both as an endocrine organ and beyond.

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REFERENCES

1. Muir R & Drummond WB 1893 *Journal of Anatomy & Physiology* **28** 125–141.
2. Scheller EL *et al.* 2016 *Trends in Endocrinology & Metabolism* **27** 392–403.
3. Scheller EL *et al.* 2015 *Nature Communications* **6** 7808.
4. Scheller EL *et al.* 2016 *Adipocyte* **5** 251–269.
5. Schwartz AV 2015 *Frontiers in Endocrinology (Lausanne)* **6** 40.
6. Gimble JM *et al.* 1996 *Bone* **19** 421–428.
7. Sulston RJ & Cawthorn WP 2016 *Hormone Molecular Biology and Clinical Investigation* **28** 21–38.
8. Shafat MS *et al.* 2017 *Blood* **129** 1320–1332.
9. Morris EV & Edwards CM 2016 *Frontiers in Endocrinology (Lausanne)* **7** 90.
10. Horowitz MC *et al.* 2017 *Adipocyte* **6** 193–204.
11. Naveiras O *et al.* 2009 *Nature* **460** 259–263.
12. Zhou BO *et al.* 2017 *Nature Cell Biology* **19** 891–903.
13. Cawthorn WP *et al.* 2016 *Endocrinology* **157** 508–521.
14. Ghali O *et al.* 2016 *Frontiers in Endocrinology (Lausanne)* **7** 125.
15. Cawthorn WP *et al.* 2014 *Cell Metabolism* **20** 368–375.
16. Kricun ME 1985 *Skeletal Radiology* **14** 10–19.

PRECISION LIFESTYLE MEDICINE IN OBESITY AND TYPE 2 DIABETES

WRITTEN BY PAUL W FRANKS

Obesity and type 2 diabetes are major global scourges, with both genetic and environmental causes. Lifestyle interventions reduce the risk of developing diabetes in high risk people, and may slow down progression once the disease is diagnosed, but there is considerable variability in response to such interventions.

Much of this may be related to variable adherence and compensatory behaviours. However, there is compelling evidence that a person's glycaemic response to food is likely to be driven by biological variants that are personal. Metabolic adaptation to exercise has also been convincingly demonstrated.

As Paul Franks explains in this article, continued emphasis on discovering biomarkers that determine individual responses to lifestyle factors will probably lead to the design of robust lifestyle interventions that are more personalised and more effective than today's standard-of-care.

Diet modification is the standard-of-care for new-onset type 2 diabetes in most western healthcare systems. However, dietary intervention alone is often insufficient to prevent the disease from progressing, and treatment with single or combined drug therapies typically ensues, eventually progressing to replacement insulin for about one-third of patients.[1]

The major global drug companies spent well over US$100 billion in 2013 on sales and marketing and on research and development.[2] Comparable statistics are unavailable for lifestyle medicine, but the level of investment is likely to be orders of magnitude less, because generating revenue from lifestyle medicine is far more challenging than for drugs, not least because patenting lifestyle 'products' is more challenging than for new molecules and pharmaceuticals, where the intellectual property rights can be clearly defined.

Despite the relatively modest funding for lifestyle medicine, the major intervention trials show that diet, exercise and weight loss can help ameliorate diabetes progression.[3] Nevertheless, there is a great deal we do not know about how lifestyle can be used to combat obesity and diabetes on an individual level, which is reflected in the modest degree (about 36 months) to which tightly controlled lifestyle interventions delay the onset of diabetes in high risk people. The impact is less in real-world studies,[3] which may be due to the unwillingness or inability of patients and their clinicians to persist with lifestyle therapy, as well as the ineffectiveness of the interventions in some patients.

Importantly, adherence and effectiveness are reciprocally related, as people who see little or no benefit are less likely to continue to adhere, and lack of adherence undermines the effectiveness of interventions. This emphasises the need to treat patients with the therapies that are best suited to their 'biotype', as well as determining how to deliver these interventions in ways that maximise long-term compliance.

EXPLORING INDIVIDUALITY

Lifestyle interventions that induce weight loss for diabetes prevention are most effective in people who are glucose intolerant (i.e. whose post-prandial glucose is elevated), and less effective in those with isolated fasting glucose.[4] This is probably due to the underlying causes of these two types of dysglycaemia: the former is attributable mainly to peripheral insulin resistance, which can often be ameliorated through weight loss, whereas the latter is primarily the consequence of excessive hepatic gluconeogenesis.

Nevertheless, sustained hypocaloric diets (around 800kCal/day) can also profoundly improve fasting glycaemia too, even in people with manifest diabetes, by virtue of reductions in liver fat content and corresponding improvements in liver insulin sensitivity.[5] The problem is that long term adherence to such diets is obviously difficult and only highly motivated patients are likely to benefit from this strategy.

The potential to improve the precision of lifestyle interventions is likely to far outweigh the potential for drug therapies in type 2 diabetes, primarily

'The potential to improve the precision of lifestyle interventions is likely to far outweigh the potential for drug therapies in type 2 diabetes, primarily because diet and exercise have wide-ranging effects on energy metabolism with few, if any, serious side effects in most patients.'

because diet and exercise have wide-ranging effects on energy metabolism with few, if any, serious side effects in most patients. By contrast, most anti-diabetic drugs target specific pathways and cannot be tolerated or cause adverse events in some patients.

The notion of optimising lifestyle interventions by designing these to fit the biological characteristics of an individual patient is predicated on there being high between-person variability and low within-person variability in the response to the components of the intervention. The measure of 'response' also needs to be clinically relevant, for which biomarkers with good predictive ability should be available, safe and scalable, if the approach is to be used in the public health setting.

There are multiple reports of high between-person variability in response to diet and exercise interventions,[6] but it is often impossible to separate true between-person response variability from error, and few studies have demonstrated that the response estimates are consistent within an individual over time. Indeed, much of the apparent variability in response to lifestyle interventions is likely to be artefactual, as discussed elsewhere.[7,8] Nevertheless, three recent studies of diet[9,10] and exercise[11] provide compelling evidence that an individual's characteristics influence the metabolic response to diet and exercise.

'Harnessing individual-level biological variant data to optimise diets has already proved valuable for the regulation of blood glucose, and may prove of further value for other diabetes-related traits, including weight change.'

THE IMPACT OF DIET

In people with diabetes, minimising variability in glycaemic response to food is a major feature of the patient's self-care regime, as very high glucose concentrations can be harmful to the insulin-producing (β-)cells in the pancreas and to the vasculature, and very low glucose can lead to loss of consciousness.

In the first of the two diet studies,[9] diet patterns and glycaemic response were observed in 800 adults during 1 week. Participants wore continuous glucose monitors, detailed information on diet was collected via a mobile app, and metagenomic sequences were obtained from stool. Within the 47,000 meals consumed during the period, one standardised meal each day (including 50g carbohydrate) was provided to each participant.

The authors observed high between-person variability in response, but relatively low within-person variability, suggesting that the glycaemic response to food is driven by personal factors. They then derived a machine learning algorithm to predict glycaemic response to each meal based on the data collected in the observational phase, and designed personalised diet interventions, to which 26 adults were randomised in order to demonstrate that a person's glucose variation can be manipulated by personalising their diets. A core feature of the algorithm was the gut microbiome sequence data.

In a follow-up study, the same group undertook a randomised trial of white and sourdough bread to determine whether this influenced clinical response parameters, including blood glucose excursions after a 75g oral glucose load.[10] Although no difference was observed in the effects of the different bread types, high variation in glycaemic response to bread was observed between individuals, with relatively low inter-individual variation. As in the earlier trial, the authors were able to derive algorithms using microbiome sequence data to predict an individual's glycaemic response to bread.

RESPONSE TO EXERCISE

There has been much written about exercise responders and non-responders and the biological basis to these adaptations.[12] One of the earliest published analyses supporting this idea came from the HERITAGE Study, an exercise intervention trial in which participants were assessed at the beginning and end of a 20-week exercise intervention.[13]

The authors reported large inter-individual variability in response to exercise for aerobic fitness adaptation, although the design of the study limited the extent to which the key sources of variability (i.e. biological variation, compliance and technical error) could be distinguished. Because the study had only one follow-up assessment (at the end of the trial), the within-individual variability in response could not be accurately quantified. Nevertheless, many have interpreted these results to mean that some people do not respond to exercise (we discuss come of the caveats underlying this interpretation elsewhere[7]).

To test the 'non-responder' hypothesis, Montero and Lundby undertook a 6-week exercise intervention, during which aerobic fitness was repeatedly assessed.[11] The authors eloquently demonstrated that some participants were highly responsive to exercise, whereas others responded with only small improvements in fitness, yet none of the participants was a true 'non-responder'.

Thus, amongst the vast literature on the biological basis of individual responses to diet and exercise, there are a few well-conducted trials that provide strong evidence that response predictors are personal, and in some instances quantifiable. Harnessing individual-level biological variant data to optimise diets has already proved valuable for the regulation of blood glucose,[9,10] and may prove of further value for other diabetes-related traits, including weight change. Such applications could prove valuable when lifestyle medicine is used to prevent or treat type 2 diabetes and obesity.

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REFERENCES

1. Centers for Disease Control and Prevention 2014 *National Diabetes Statistics Report* www.thefdha.org/pdf/diabetes.pdf.
2. Swanson A 2015 *The Washington Post* http://wapo.st/2zb4kpu.
3. Terranova CO *et al.* 2015 *Diabetes Obesity & Metabolism* **17** 371–378.
4. Zhang X *et al.* 2017 *Diabetes Research & Clinical Practice* **123** 149–164.
5. Steven S *et al.* 2016 *Diabetes Care* **39** 808–815.
6. Bohm A *et al.* 2016 *Endocrine* **51** 390–401.
7. Franks PW & Poveda A 2017 *Diabetologia* **60** 784–792.
8. Mutie PM *et al.* 2017 *BMC Medicine* **15** 171.
9. Zeevi D *et al.* 2015 *Cell* **163** 1079–1094.
10. Korem T *et al.* 2017 *Cell Metabolism* **25** 1243–1253.
11. Montero D & Lundby C 2017 *Journal of Physiology* **595** 3377–3387.
12. Sparks LM 2017 *Diabetologia* **60** 2329–2336.
13. Bouchard C & Rankinen T 2001 *Medicine & Science in Sports & Exercise* **33** Suppl 6 S446–S451, discussion S452–S453.

LIPODYSTROPHY: LIFE WITHOUT FAT

WRITTEN BY JAKE P MANN & DAVID B SAVAGE

Fat receives a lot of bad press, but patients with lipodystrophy exemplify its critical physiological importance. Lipodystrophy is characterised by the functional failure of fat, usually associated with its anatomical absence (lipoatrophy). Though a comparatively rare condition, it is relevant to many endocrinologists/diabetologists, as it highlights the metabolic role of fat in surplus energy storage and has contributed to a deeper understanding of human insulin resistance, non-alcoholic fatty liver disease, and type 2 diabetes.

Lipodystrophies are a relatively heterogeneous group of conditions that can be broadly classified into congenital or acquired, and partial (limited to certain areas of the body) or generalised.[1,2]

Congenital (generalised) lipodystrophies are the most extreme forms.[3] They are autosomal recessive disorders that typically present in children who have almost no adipose tissue. In addition, there are several forms of familial partial lipodystrophy, most of which are inherited in an autosomal dominant fashion. These are often said to present around puberty, but this may be related to the fact that they become more clinically obvious in girls at this stage, as they frequently manifest as a lack of lower limb and femorogluteal fat.

Acquired partial lipodystrophy (APL) is more common, typically progresses in a cephalocaudal pattern, and is not usually associated with metabolic problems (though it can be) but it is often associated with C3 nephritic factor and glomerulonephritis. APL may occur secondary to drugs (for example, anti-retrovirals in treatment of HIV) or in association with other autoimmune disorders. Similarly, acquired generalised lipodystrophy is often associated with other autoimmune problems.

PRESENTATION OF LIPODYSTROPHY

The lack of subcutaneous fat in congenital generalised lipodystrophy is immediately obvious: patients may appear strikingly muscular and progerioid due to reduced facial fat. However, partial lipodystrophy may not be immediately apparent, and the lack of adipose may be most evident on the thighs, buttocks and upper arms.[4] Other signs that may be found are acanthosis nigricans (reflective of severe insulin resistance), hepatomegaly (due to hepatic steatosis) with splenomegaly (from portal hypertension) and, in some cases, pseudoacromegalic features. Women frequently present with manifestations of polycystic ovary syndrome.

Biochemically, patients have all the features of the metabolic syndrome: hyperglycaemia, dyslipidaemia and raised liver enzymes due to fatty liver. They have high insulin levels, driven by severe peripheral insulin resistance, and low leptin and adiponectin levels (variable depending on the extent of lipodystrophy), due to a lack of functional adipocytes and severe insulin resistance.

Patients with lipodystrophy often display the same metabolic features that are expected in obese people: type 2 diabetes, premature coronary artery disease, stroke and non-alcoholic fatty liver disease.

TREATMENT

Medical treatment is similar to that of obese patients with the metabolic syndrome, with dietary restriction the mainstay of treatment. Patients often require high doses of insulin (>2IU/kg per day, for example) to achieve euglycaemia. However, this can be significantly improved if leptin therapy is initiated[5] in those with low leptin levels (a specific cut-off has yet to be agreed, but levels below 5μg/l in men and 10μg/l in women can be used as a rough guide). Leptin, whilst not yet approved in the EU, is likely to become the first-choice therapy in patients with generalised lipodystrophy, whereas its use in patients with partial lipodystrophy requires further investigation.

Bariatric surgery has also been shown to be very effective in familial partial lipodystrophy, where patients are hyperphagic and excess intake accelerates their metabolic complications. Common causes of death are cardiomyopathy, macrovascular atherosclerotic disease, and cirrhosis secondary to fatty liver.

UNDERLYING PHYSIOLOGY

Mammals have evolved to cope with sizable fluctuations in nutrient supply by storing excess energy in macromolecules. For a non-obese 70kg man, liver and muscle glycogen stores hold only about 6MJ of energy, whereas adipose tissue stores contain about 600–800 MJ as triacylglycerol (around 100-fold more than glycogen stores).

Adipocytes are 'professional' storage cells that contain triacylglycerol within a huge single lipid droplet. However, there is a limit to their expandability, both in terms of cellular hypertrophy and hyperplasia. Once surpassed, excess lipid accumulates in so-called ectopic sites such as the liver and muscle. These tissues are less well-adapted to cope with excess lipid, which tends to impair insulin action.[6] This hypothesis is often referred to as the 'adipose overflow hypothesis'.

'Patients with lipodystrophy often display the same metabolic features that are expected in obese people: type 2 diabetes, premature coronary artery disease, stroke and non-alcoholic fatty liver disease.'

Patients with lipodystrophy have severely limited adipose expandability; therefore this is manifest at a normal or even low body mass index. The 'metabolically healthy' obese continue to expand their adipose storage capacity, but if and when they reach their 'genetically defined' limit, they will manifest type 2 diabetes and fatty liver. It has very recently been shown that adipose expansion capacity is genetically determined, varies in adults, and is associated with dyslipidaemia and hyperinsulinaemia.[7] Some adipose depots are of particular importance, particularly the thighs and buttocks, which is supported by evidence that a low hip circumference (separately from a high waist circumference) is a marker of metabolic risk.

LESSONS LEARNT FROM LIPODYSTROPHY

The most important principle gleaned from lipodystrophy is that weight loss is the most effective treatment for the metabolic syndrome, as it reduces the energetic load on adipocytes. This is amply demonstrated by the dramatic clinical benefits, including reversal of type 2 diabetes, associated with extreme calorie restrictive diets[8] or bariatric surgery.[9]

It is also the mechanism underlying the action of peroxisome proliferator-activated receptor (PPAR) agonists such as the thiazolidinediones (TZDs), which expand adipocyte storage capacity. Patients often gain weight (and fat mass) in response to TZDs, but that's how they work. Fat should not be seen as the enemy, but increasing evidence suggests that its capacity to expand in response to sustained excess energy intake is finite and, when exceeded, serious metabolic disorder ensues.

'Many obese patients with the metabolic syndrome mimic lipodystrophy because their adipocytes are "full", and the best treatment is to "empty" them by weight loss.'

Therefore, whilst lipodystrophy is relatively rare, it highlights the importance of 'healthy fat'. Making the diagnosis is very useful as it may inform predictive genetic testing in families and therapeutic decisions which can be life-transforming, at least in terms of metabolic control. Many obese patients with the metabolic syndrome mimic lipodystrophy because their adipocytes are 'full', and the best treatment is to 'empty' them by weight loss.

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REFERENCES

1. Garg A 2011 *Journal of Clinical Endocrinology & Metabolism* **96** 3313–3325.
2. Robbins AL & Savage DB 2015 *Trends in Molecular Medicine* **21** 433–438.
3. Van Maldergem L *et al.* 2002 *Journal of Medical Genetics* **39** 722–733.
4. Parker VER & Semple RK 2013 *European Journal of Endocrinology* **169** R71–R80.
5. Oral EA *et al.* 2002 *New England Journal of Medicine* **346** 570–578.
6. Samuel VT & Shulman GI 2016 *Journal of Clinical Investigation* **126** 12–22.
7. Lotta LA *et al.* 2017 *Nature Genetics* **49** 17–26.
8. Lim EL *et al.* 2011 *Diabetologia* **54** 2506–2514.
9. Mingrone G *et al.* 2012 *New England Journal of Medicine* **366** 1577–1585.

THE BROWNING OF WHITE FAT

WRITTEN BY MARK CHRISTIAN

The process of 'browning' white adipose tissue (WAT) has become a key focus area in research, due its fat burning potential for obesity treatment.

Functional brown adipose tissue (BAT) has been identified in adult humans by positron emission tomography–computed tomography (PET-CT) scans, as its high requirement for energy substrate instigates the rapid uptake of radiolabelled glucose. The substantial energy needs of BAT are a consequence of its unique property of heat production by adaptive thermogenesis. This process mediates the breakdown of energy substrates without the generation of ATP. Therefore, energy dissipation by BAT has the capacity to control obesity by diverting excess fat into heat production.

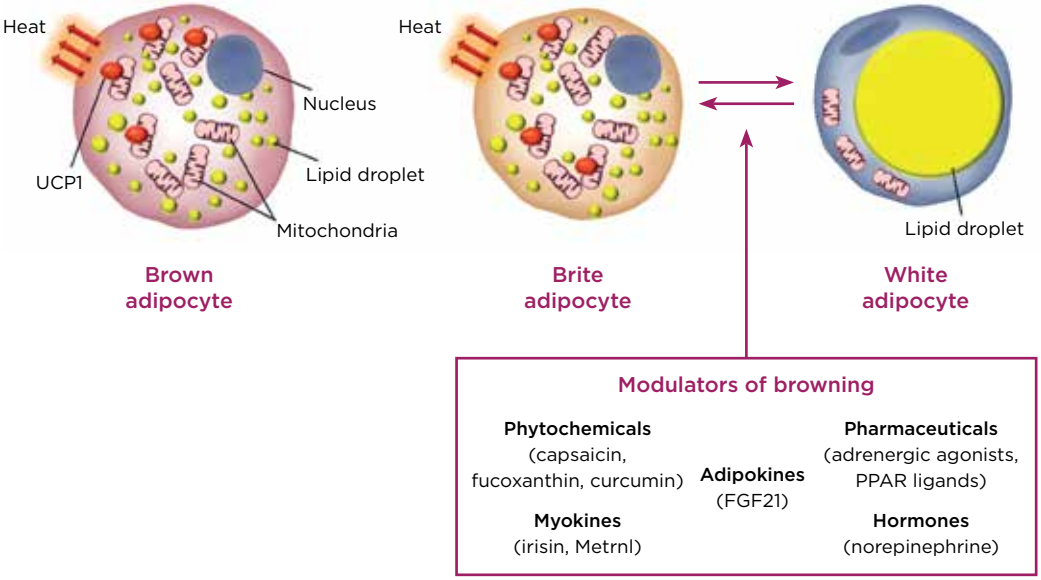
Adipose tissue comes in two main types: WAT, which is the primary site of energy storage, and BAT, which stores lower levels of fat and can be activated to oxidise fatty acids to maintain body temperature. These tissues are composed mainly of white and brown adipocytes respectively.

Whereas brown adipocytes contain many mitochondria and many lipid droplets (multilocular), white adipocytes have few mitochondria and a single large lipid droplet (unilocular). Importantly, uncoupling protein 1 (UCP1) is present exclusively on the inner mitochondrial membrane of brown adipocytes where it uncouples the respiratory chain from ATP generation.

DYNAMIC ADIPOSE TISSUE

Adipose tissue is incredibly dynamic and responds to stimuli including external environmental and dietary cues. The plasticity of WAT is demonstrated by a large increase in the number of brown adipocyte-like cells, termed beige or brite (brown-in-white) adipocytes, upon sustained cold exposure or direct β-adrenergic activation.

The WAT-resident brite adipocytes induced by the 'browning' stimulus are phenotypically similar to the classical brown adipocytes in BAT, having many mitochondria, multilocular lipid droplets and expressing UCP1. Evidence suggests that brite adipocytes may contain comparable amounts of UCP1 to BAT-resident brown adipocytes, indicating that they may have similar thermogenic capacities.



The three distinct types of fat cell and examples of agents that 'brown' white adipocytes (FGF21, fibroblast growth factor-21; PPAR, peroxisome proliferator-activated receptor). ©M. Christian

INTERCONVERSION OF WHITE AND BRITE ADIPOCYTES

Elegant lineage tracing studies have revealed a remarkable property of adipocytes in WAT. White adipocytes within the subcutaneous WAT depot were found to reversibly convert to brite adipocytes. Furthermore, whereas classical brown adipocytes share a common Myf5-expressing precursor with muscle cells, brite fat cells derive from both Myf5-negative and -positive precursors. The white–brite adipocyte transdifferentiation events are evident at the gene expression and morphological levels, with reversible transitions between the appearance of unilocular and multilocular lipid droplets. These findings illustrate that the remodelling of WAT to gain and lose BAT properties is facilitated by profound changes within existing differentiated adipocytes.

PATHWAYS TO INDUCE BROWNING

The most studied pathway known to induce the browning of white adipocytes works through the actions of norepinephrine. This is released from sympathetic nerve endings and acts on β-adrenergic receptors on the surface of adipocytes. In addition, cold exposure increases secretion of the myokine irisin and the brown adipokine fibroblast growth factor-21 (FGF21). An additional exercise- and cold-induced myokine hormone (meteorin-like; Metrnl) was recently discovered. These secreted factors promote browning of white adipocytes and represent connections between muscle, BAT and WAT, orchestrating cold-induced adaptive thermogenesis.

Although UCP1 expression is a main characteristic of brite cells and routinely used for identifying browning of WAT, other essential events occur during this process, such as mitochondrial biogenesis and increases in the cellular capacity for glucose and fatty acid uptake and oxidation. The genes and pathways that determine the key functional and morphological differences between white and brite adipocytes are yet to be fully elucidated.

We adopted a strategy to define the brite transcriptome by comparing the expression profiles of BAT and WAT depots. To achieve this, a set of genes was identified as enriched in BAT versus WAT (from mice at thermoneutrality), as well as increased in WAT by cold exposure. This analysis confirmed the induction of the BAT genes *Ucp1*, *Cidea*, *PGC-1a*, *Plin5* and *PPARa* associated with the browning of adipose tissue. Additional genes that are part of the brown/brite transcription fingerprint include the fatty acid receptor *Gpr120*, the regulator of G protein signalling *Rgs7* and signalling factor *Nrg4*. These findings highlight potentially important signalling differences between white and brown/brite adipocytes.

NEW APPROACHES FOR BROWNING WAT

The discovery of brite adipocytes in humans has attracted research interest in identifying pharmacological and nutritional browning activators with metabolic benefits. Strategies include up-regulating sympathetic input into WAT, increasing the sensitivity and/or amount of adrenergic receptor in WAT, and manipulating key transcription factors in the browning process.

Studies in humans have shown that highly β_3-selective adrenergic agonists such as mirabegron, a drug approved for treatment of overactive bladder, may increase energy expenditure with greatly reduced cardiovascular side effects compared with other sympathomimetic drugs. Phytochemicals such as the flavonoid curcumin found in turmeric promotes browning. Also, dietary capsaicin and capsinoids promote WAT browning through activation of vanilloid receptors. Similarly, fucoxanthin, from algae, and fish oil (rich in ω3 polyunsaturated fatty acids) can also induce UCP1 expression in WAT by upregulating β_3-adrenergic receptor expression and consequently enhancing WAT sensitivity to adrenergic stimulation in adipocytes.

Novel approaches include re-examining the browning actions of drugs that have already been approved, such as exenatide and sildenafil (originally designed for type 2 diabetes and erectile dysfunction treatment respectively), which are subject to testing of their browning effect in phase 4 clinical trials. Such novel therapeutic strategies have the potential to treat obesity and the range of associated diseases that represent a profound burden on healthcare systems.

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FAQs (FAT ACCUMULATION AND QUALITY) IN NON-ALCOHOLIC STEATOHEPATITIS

WRITTEN BY MICHAEL ALLISON & MICHELE VACCA

The first question you may ask is 'Why are we discussing non-alcoholic steatohepatitis (NASH) in *The Endocrinologist*?' Fatty liver (steatosis) is found in 15–30% of the adult population. The commonest cause is insulin resistance, which is associated with metabolic syndrome and type 2 diabetes. An accumulating body of evidence links adipose tissue expandability defects and inflammation with non-alcoholic fatty liver disease (NAFLD); the metabolic milieu (glucose and insulin) drives enhanced *de novo* lipogenesis within hepatocytes and the accumulation of lipotoxic intermediates, thereby exacerbating liver damage.

WHAT ARE THE TERMINOLOGY, DIAGNOSIS AND CONSEQUENCES?

NAFLD is the term describing the whole spectrum of this condition. Steatosis describes simple fat accumulation within hepatocytes, whereas NASH refers to the presence of fat associated with inflammatory infiltrates and fibrosis (see Figure).

Differentiating between 'benign' steatosis and NASH remains difficult. Despite extensive work on imaging tools and non-invasive biomarkers, the gold standard continues to be liver biopsy. Natural history data indicate that NASH, as opposed to steatosis, can progress to advanced liver disease, with risk of liver cancer and liver failure necessitating liver transplantation. The relevance of NASH as a cause of cirrhosis is demonstrated by the fact that NASH-related cirrhosis will soon become the commonest indication for liver transplantation.

DOES YOUR PATIENT HAVE SIGNIFICANT LIVER DISEASE?

Given the prevalence of NAFLD in the population, one of the major challenges is determining who has NASH with significant fibrosis. A number of staging algorithms based on blood tests and simple clinical parameters have been developed with this in mind, but those currently available are imperfect.

Simple tools such as FIB-4 (Fibrosis-4) or the NAFLD Fibrosis Score, which incorporate factors such as age, AST (aspartate aminotransferase), ALT (alanine aminotransferase) and platelet count, as well as the presence/absence of diabetes or impaired glucose tolerance, have been found to be most useful as a means of excluding significant NASH in patients with a score below a defined threshold. Additional methods of assessing individuals within the NAFLD spectrum include imaging modalities determining liver stiffness, most commonly using transient electrography (e.g. Fibroscan); this correlates with the amount of fibrosis.

Experts in the field recommend focusing on patient groups at high risk of significant liver disease, rather than assessing people based on the abnormality of liver function tests. Patients with diabetes are at significant risk of having active NASH with progressive fibrosis, as well as a twofold increased risk of liver cancer. As such, assessment of liver disease should be introduced into the regular assessment of type 2 diabetic patients in the same way that other comorbidities (e.g. retinopathy, neuropathy and nephropathy) are routinely assessed. Close links between primary and secondary care diabetes services and hepatology services, and shared pathways for the management of these subjects, are thus highly recommended.

IS THERE AN EFFECTIVE TREATMENT?

Weight reduction achieved through programmes of lifestyle revision or bariatric surgery is the most effective treatment in NASH. There is a good rationale for the pharmacological management of the underlying metabolic disease (including insulin sensitisers like metformin or pioglitazone, and liraglutide) and antioxidants (e.g. vitamin E), but no generally accepted treatment to improve liver histology in the long term. Although controversial, we believe that insulin therapy should be reserved for late stage diabetes if NASH coexists, to avoid excessive hepatic lipogenesis.

Having previously been a frustrating area to treat, long term phase 3 studies are currently being undertaken to examine the effectiveness of agents including other glucagon-like peptide-1 receptor agonists, farnesoid X receptor agonists, peroxisome proliferator-activated receptor (PPAR) α/δ agonists, and anti-inflammatory and anti-fibrotic drugs. In addition, other molecules in earlier phase studies are targeting metabolic and inflammatory processes. This rapidly changing landscape means that it will be increasingly important to diagnose/stage NASH.

MICHAEL ALLISON
NASH Service, Liver Unit, Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge, UK

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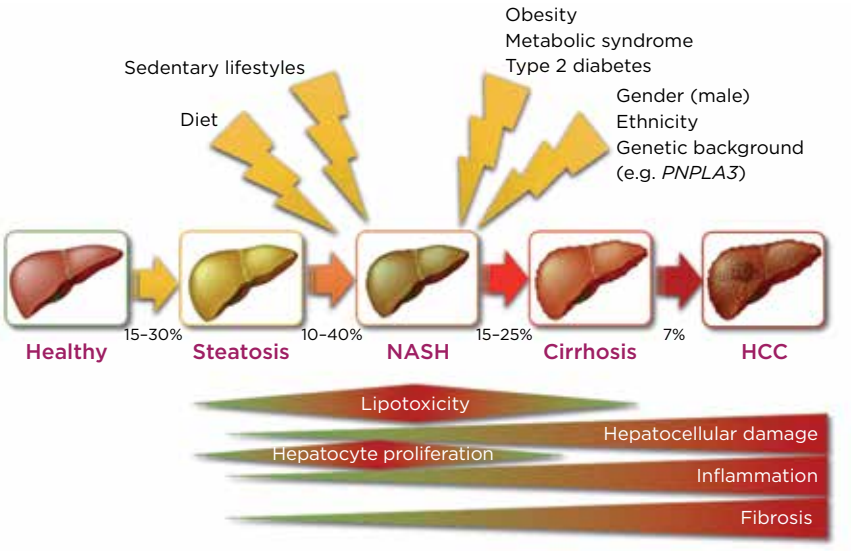
Stages and pathophysiology of NASH (HCC, hepatocellular carcinoma). ©M. Allison & M. Vacca



DON'T KNOW MUCH BIOLOGY...

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Like me, you have probably been giving serious thought to the representation of the life sciences in popular song.

There are, of course, many easy parallels to draw between the pop music business and science. Pop music was once famously full of man-child mavericks, delighted to defenestrate televisions, to dunk Daimlers in swimming pools, and to repeatedly overindulge and overdose. But rather than being the new rock and roll, science got there first.

Pick up any book on the history of science and marvel at how past (almost always male) researchers happily dosed themselves with *Helicobacter pylori* (to demonstrate how stomach ulcers were caused) or LSD (to enjoy the bike ride home), and forced needles under their eyeballs (to investigate the perception of colour) or themselves into decompression chambers (to study the effects of various gases).

JBS Haldane (for indeed, 'twas he who entered the decompression chamber) subsequently suffered from seizures and burst eardrums, but commented that 'The drum generally heals up ... if a hole remains in it, although one is somewhat deaf, one can blow tobacco smoke out of the ear in question, which is a social accomplishment.'

We rarely encounter such cavalier attitudes nowadays. Pop musicians and scientists typically own intact televisions and eardrums, and both industries often stand accused of encouraging unoriginal conformists and yes-men, to the detriment of true creatives.

Pop music and science can both also be said to have very poorly mapped out career structures, and might both be described as 'formulaic', albeit in different senses.

These parallels have sadly not fostered the culture of mutual respect between disciplines that one might expect. Pop simply does not give biology the props it deserves.

'Rather than being the new rock and roll, science got there first.'

Sure, prog rock titans like to steal scientific ideas upon which to hang concept LPs. For example, Rush's 'Natural science' paddles through both biology and astronomy, describing how the ebbing tide '...leaves a trail of tidal pools/In a short-lived galaxy' in which live '...busy little creatures/ Chasing out their destinies'. Less pompous, but only marginally less excruciating, is a song by Genesis on combatting the terrors of the invasive giant hogweed. This advises 'Strike by night!/They are defenceless/They all need the sun to photosensitise their venom'.

More recently, Girls Aloud seemed pleased that 'You can't mistake my biology' (in a track from the album 'Chemistry', no less), and followed this up with details of their own interests in linguistics and gait analysis ('The way that we talk/The way that we walk'). And I also have a soft spot for the interface of science and pop in Bobby Sheen's northern soul classic, 'Dr Love' ('And in Love-ology, yeah/I have a ... a PhD!').

Typically, however, artists take their cues from Sam Cooke, who seems wistfully proud when he croons 'Don't know much biology' (or 'about a science book', for that matter). Belle and Sebastian show their artsy bias when they quickly follow 'We do chemistry, biology and maths...' with 'I want poetry and music and some laughs'.

How can we convince the world of pop that science and laughs are not mutually exclusive? Perhaps we can make use of that most rock and roll of specialties, endocrinology. The age-old obsession of pop with the young, exciting, sex-obsessed and devil-may-care is usefully encapsulated in the popular use of the word 'hormones'.

Who would quibble with Motorhead's Lemmie, when he grunts 'Dance, get your hormones fired', that he does not apprehend the complexity of hormone release kinetics? When Christine Aguilera has made the effort to comment on the time course of endocrine effects, what kind of nit-picker would suggest that her understanding of relativity is in need of a polish when she sings of 'hormones racing at the speed of light'? And who dares to suggest to Missy Elliott that, when she boasts (in obvious reference to the inherent pulsatility of many endocrine systems) 'my hormones are jumpin' like a disco', that, in fact, hormones don't jump?

'The age-old obsession of pop with the young, exciting, sex-obsessed and devil-may-care is usefully encapsulated in the popular use of the word "hormones".'

As regards specific hormonal systems, the male hypothalamo-pituitary-gonadal axis has the biggest fan base. In the elegiac 'Where did my spring go?' by the Kinks, Ray Davies plaintively enquires 'Where did my hormones go?' and then, mentally connecting this to the role of dihydrotestosterone in male pattern baldness, asks 'Where did my hair go?' Artists as diverse as Sia, Bush and The Descendents have songs named 'Testosterone', and rap and grime braggadocio is awash with examples, from Dizzee Rascal to Rick Ross to Method Man, equating manliness with their own circulating levels of sex steroids.

However, misapprehensions remain. When RZA of the Wu Tang Clan claims 'My testosterone stimulate her oestrogen' we can only assume that he, no doubt familiar with the aromatase enzyme, has become confused over its precise role. We in the endocrine community must continue to work hard to ensure endocrinology is as accurately represented in chart topping hits as it is in our own scientific papers. To paraphrase Woody Guthrie, we must convince the public that 'This gland is your gland'...

KEVIN G MURPHY
Division of Endocrinology and Metabolism, Department of Medicine, Imperial College London, UK

Society for Endocrinology

Renewing that's plain sailing

It's time to renew your Society membership for 2018 and it takes just a few simple steps.

All you have to do is log into the Members' Area and click renew!

Discover some of the great benefits available to you in 2018!

www.endocrinology.org/membership

Interdepartmental peer review
WHAT'S IN IT FOR YOU?

WRITTEN BY ANTONIA BROOKE

The Society's Interdepartmental Peer Review scheme is a voluntary, supportive and non-confrontational review of endocrine services. The scheme was inspired by John Wass (Oxford) when he was Chair of the Society for Endocrinology's Clinical Committee in 2002, set up by the Society for Endocrinology, led by John Bevan (Aberdeen) and then Petros Perros (Newcastle upon Tyne).

The scheme allows both a subjective and objective look into a centre's achievements and difficulties. The idea of the programme is to ensure safe and sustainable services and facilitate improvements, negotiating a difficult financial climate. It focuses on the clinical care process and organisational aspects of care, and promotes examples of exceptional practice.

The current peer review programme is undergoing change, and I have been given the opportunity to continue the work of Petros Perros to develop the programme further with the assistance of the peer review team.

WHAT ARE THE ADVANTAGES OF PARTICIPATING?

Peer review can help support the changes that are most wanted by endocrine units, paying attention to local NHS priorities for change. It is an opportunity to reflect on current practice, build morale within the team and recognise the centre's achievements, whilst benchmarking against national data. It also provides a platform to reassure patients that there has been external validation and to promote the specialist service within the trust. Appraisal and sharing ideas with experienced clinical endocrinologists are important, and 100% of centres that have participated have found it useful.

With an ambition to review all specialist endocrinology centres in the UK, there is a great opportunity for exchanging ideas, which will help strengthen the specialty, improve networking and promote good practice.

WHAT IS THE FUTURE OF PEER REVIEW?

It is recognised that centres offer a range of routine, specialist and super-specialist endocrinology and don't always follow a binary model between the nearest 'tertiary centre' and 'secondary care'. To reflect this continuum, the traditional model of pairing a 'tertiary' centre with a 'district general hospital' has been replaced to allow single centres to be reviewed.

The self-assessment questionnaire has been streamlined to acknowledge the time pressures in current clinical practice, and there is a timeline of up to 3 years for planning visits, to allow an adequate period for preparation and identifying appropriate reviewers. The focus has changed to put more emphasis on clinical outcomes, and links to other quality measures are being established. There will also be development of a platform through the Society for Endocrinology to share resources and experiences and promote good practice and ideas.

WHAT DETERS CENTRES FROM BEING REVIEWED?

There continues to be enthusiasm about being peer reviewed and the importance of the process. The main concern about participating has been the amount of time and hard work that are perceived to be involved in gathering the data, in services which are already stretched. The self-assessment questionnaire has been refined to reflect this. Tristan Richardson, who has recently been through the process in Bournemouth, said that data gathering took around 8 hours for two consultants, plus nurse time and support from the management team. Again, having a focus within a realistic time frame allows the data to be gathered without tight deadlines, and the benefits of being reviewed make it worth the effort.

There is also a misconception that centres must 'put their house in order' before they are peer reviewed. Reviewing the services when a newly recruited consultant comes to the department can help strategy. Setting a future timeline helps focus on the necessary changes and a realistic time to achieve them. Even if targets are not met prior to peer review, the report can help reflect some of the difficulties that the departments have struggled with, as a mechanism for helping achieve change.

WHO HAS BEEN PEER REVIEWED?

The hospitals that have been peer reviewed are shown at **www.endocrinology.org/clinical-practice/interdepartmental-peer-review**. Their catchment areas range from 280,000 to 2.5 million, and they see between 267 and 1,530 new referrals per year. Of the centres reviewed, 100% felt it was worthwhile and would volunteer again. There was a similar level of satisfaction from reviewers and a great deal to be learnt from sharing practice.

PEER REVIEW FEEDBACK

> "I believe the visit was very important – our MD and CEO used the report to lobby primary care trusts whenever they had a chance."

> "It actually took less time than I thought to do the self-assessment questionnaire! The time has not been excessive and it has facilitated our concentrating on ourselves, which often you don't get the time to do."

> "Excellent report captured all the current issues within our department and the city as a whole."

> "Many thanks to the reviewers for their supportive attitude and for stimulating discussion."

> "We often feel a bit isolated … so it was reassuring to learn we're actually doing quite well!"

> "Already achieved some focus on areas for development, but probably even more crucially has allowed us to resist additional pressure to take on further general internal medicine commitments at the expense of specialty."

> "Enabled some deficiencies to be highlighted to colleagues in multi-disciplinary teams – i.e. a lever for change."

> "We have had two new consultants, and one retirement. It was useful to have the review at a time of change to help us prioritise service development."

> "This has been a very worthwhile experience and is highly recommended. It is non-threatening, constructive and informative, delivered with understanding of what the real issues at the grass roots of clinical care are."

HOW IS THE PEER REVIEW ASSESSMENT MADE?

Preparation for the visit involves filling in a self-assessment questionnaire about the centre and gathering relevant documents and protocols. The visit then occurs over the course of a day, and is conducted by two experienced clinical endocrinologists and two senior endocrine nurse specialists. The reviewers would be matched as closely as possibly for suitability to the centre. The peer review team will visit the facilities and interview clinical, secretarial and managerial staff and key clinicians of allied specialties. The quality of care is then reviewed according to set standards.

The degree of specialisation of services, the quality of interaction across departments and the ability to work with other endocrine teams locally, regionally and nationally will be assessed, with a strong emphasis on evidence of a patient-centred service. There is an opportunity to compare the data acquired with national statistics to allow benchmarking of structure of services and number of patients seen.

The report is tough and thorough. Not all of the essential standards, and only around half of the desirable standards, have been met by centres that have been reviewed, so there is still work to be done, but there are many examples of excellent practice to celebrate. All reports are confidential, but there is a chance to highlight areas of specialist expertise to enhance collaboration across networks.

LOOKING FORWARD

I am indebted to Petros Perros for leaving solid foundations, upon which I can build with the peer review team. As mentioned above, we have recently conducted a review in Bournemouth, where colleagues found it extremely useful for clinical practice. Plymouth, St Thomas' Hospital and Chelsea and Westminster Hospital have all expressed an interest in being next. This is, by definition, a collaborative effort and relies on endocrinologists and centres stepping forward to be reviewed and to be reviewers. I have no doubt that there are huge amounts to learn from each other and I look forward to the opportunity to be able to highlight good practice through the individual trusts and the Society for Endocrinology in the future.

If you would like further information about being reviewed or becoming a reviewer please contact Natasha Archer at the Society for Endocrinology (**natasha.archer@endocrinology.org**) or Antonia Brooke at the Royal Devon and Exeter Hospital (**antonia.brooke@nhs.net**). See also the Society webpage, **www.endocrinology.org/clinical-practice/interdepartmental-peer-review**.

ANTONIA BROOKE
Clinical Lead for Peer Review – Endocrinology,
Royal Devon and Exeter Hospital, UK

What it takes
TO BRING YOU SfE BES

Our annual flagship event is the highlight of the Society calendar. This year we saw 1,100 attendees in Harrogate. A huge number of people take a lot of time planning to make sure we consistently bring you the best cutting-edge endocrinology, for an enjoyable event that runs like clockwork. This is what it takes for each event...

3 years
of planning

3,000 hours
of organising
venue, programme, abstracts, registrations, exhibition, sales, marketing, press, IT, finance

22 hours
of committee meetings

Around
200 hours
of Programme Secretary time

92 markers
and
15 judges
for the hundreds of submitted abstracts

Around **150** symposium suggestions

Up to **40** onsite organisers

And also...

3 rolls
of Velcro

680 litres
of coffee

120 metres
of signage

Around **£500,000** of costs, with about **£13,000** net cost to the Society (after income from delegate fees and sponsorship)

Based on figures from 2016 event

FIND MORE ONLINE

You can get the latest Society events and training information at: **www.endocrinology.org/events**

SAVE THE DATE

Society for Endocrinology BES 2018
Glasgow, UK, 19–21 November
www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2018

Society grants to boost your LAB SKILLS AND FUND ESSENTIAL EQUIPMENT

PRACTICAL SKILLS GRANT

Your chance to learn, anywhere in the world

Up to **£1,000** to learn a new technique, conduct experiments or attend a workshop

Over **£30,000** paid out since 2014

Society members have visited **12** countries **WORLDWIDE**

©Shutterstock

2 CHANCES to apply each year: April and October

> ***It was an invaluable experience, working in different research environments and interacting with colleagues from different specialties, which has led to a new collaboration.*** Douglas Gibson, University of Edinburgh (travelled to Australia)

> ***This technique is only carried out in a small number of labs. It was extremely beneficial to spend time in the lab discussing, watching, practising and trouble-shooting.*** Naomi Brooks, University of Stirling (travelled to South Africa)

EQUIPMENT GRANTS

To obtain the tools of your trade

Apply by **23 May 2018**

Up to **£10,000** to buy, or part buy, essential lab equipment

Over **£49,000** awarded since 2015

> ***The award has enabled my research group to establish research techniques which are essential for the successful completion of our proposed research project, as well as a range of other endocrine-related projects.*** Astrid Hauge Evans, University of Roehampton

> ***The Equipment Grant has been extremely beneficial in establishing my own research laboratory, and in establishing the necessary methodologies to develop a novel area of research.*** Paul Newey, Ninewells Hospital and Medical School, Dundee

> ***The equipment was integral to enabling a successful application for a faculty-funded PhD student.*** Adam Sharples, Keele University

> ***As a new lecturer, the Equipment Grant helped me further develop my scientific career as an independent group leader. This grant funded this specific project, but also enhanced the overall quality of my group's research.*** Javier Tello, University of St Andrews

You can learn more about all Society grants and awards at **www.endocrinology.org/grants-and-awards**.

Society for Endocrinology

16–18 April 2018

Endocrine ACADEMY

Hilton Birmingham Metropole NEC, Birmingham

Including:

Endocrine Nurse Update
16–17 April 2018

Clinical Update
16–18 April 2018

Career Development Workshop
16–18 April 2018

www.endocrinology.org/events

The Endocrine Academy is designed to provide clinicians, scientists and nurses with an in-depth programme to help develop their careers and build relationships with those working in the field.

Endocrine Nurse Update is a two-day residential course for specialist endocrine nurses featuring interactive sessions, combined lectures, workshops and networking opportunities.

Clinical Update is a three-day residential course comprising lectures and interactive workshops. The small group workshops (50 delegates maximum) are targeted to specific topics on the curriculum.

Career Development Workshop is designed to meet the needs of basic scientists and clinician scientists, who are investing in building a career in academic research.

Extra special: *ENDOCRINE-RELATED CANCER* MARKS RESEARCH MILESTONES

It's been a busy time for the Editors of Society journal *Endocrine-Related Cancer*. They've been working hard to compile a swathe of special issues, with most focusing on anniversaries of significant discoveries in the field.

The September 2017 issue, guest-edited by Karen Crasta and Ritu Aneja, celebrated 50 years of research on tubulin and cancer. This was swiftly followed by the 20th anniversary of MEN1 in the October issue, guest-edited by Frank Weber and Lois Mulligan. A further special issue on MEN2 is due for February 2018.

The December 2017 issue covers the hot topic of immunotherapy and cancer, in an issue guest-edited by Laura Sterian Ward and Joanne Ngeow.

Finally (phew!), 2018 sees the 65th anniversary of the discovery of the double helix. A special issue will discuss the impact of genomics and new technologies in endocrine cancer research and care, guest-edited by Editor-in-Chief Charis Eng, William Foulkes and Jérôme Bertherat.

KEEP YOUR CAREER SWEET: THE FIRST NATIONAL DIABETES AND ENDOCRINOLOGY TASTER DAY

WRITTEN BY LOUISE HUNTER & SHAZIA HUSSAIN

'Gastroenterologists drive mud-splattered Land Rovers, cardiologists prefer fast red Ferraris, and nephrologists like amphibious vehicles. But, as an endocrinologist, you can drive **all** the cars!'

With an amusing yet inspirational speech, Tahseen Chowdhury (London) opened our first National Taster Day for clinical careers in diabetes and endocrinology, which was held in Birmingham in September.

This joint initiative by the Society for Endocrinology and the Young Diabetologists' and Endocrinologists' Forum (YDEF) aimed to showcase what's best about our brilliant specialty. It targeted trainees early in their medical careers.

Preliminary research led by Amar Puttanna (YDEF Chair) has demonstrated that a lack of exposure may deter trainees from considering a career in endocrinology and diabetes.[1] Recognising that there are few specialty events geared towards undifferentiated trainees, a group of six registrars with varying sub-specialty interests came together from across the country. They had a common goal in mind: to enhance knowledge of our specialty. To achieve this, they provided a unique opportunity for senior medical students and undifferentiated clinical trainees to see, for themselves, what our job involves.

We offered free attendance to UK students and trainees (foundation and core medical), and are hugely grateful to the local training programme directors and administrators who helped us publicise the event. Although we were unable to reimburse travel expenses, we did offer attendees a free 3-month Passmedicine subscription (**www.passmedicine.com**) as an added incentive.

THE DAY DAWNS

After months of planning, we were delighted to welcome over 70 delegates to Birmingham's Queen Elizabeth Hospital on a rainy Saturday morning. Here they gathered under the same roof as expert patients, excited members of the multidisciplinary team and enthusiastic senior clinicians. We were particularly impressed by the diverse mix of delegates, some of whom had travelled from as far as Gateshead and Southampton – and one even attended pre-nightshift!

The Faculty. ©L. Hunter & S. Hussain

The day began with a series of short talks, after which the delegates rotated through small group workshops chaired by patients and different healthcare professionals. Activities included:

- learning about a week-in-the-life of an endocrinologist from Claire Higham (Manchester)
- hearing acromegaly anecdotes from John Wass (Oxford)
- meeting Kristien Boelaert (Birmingham) and some of her patients
- experiencing hands-on insulin pump teaching led by Peter Hammond (Harrogate) and his assistant Dipsy the Teletubby
- learning to carb-count with dietician Will Hadfield (London)
- hearing the patient perspective from type 1 diabetes blogger and campaigner Georgia Thomson (Cardiff).

There were also plenty of opportunities for delegates to speak to faculty members about the wide opportunities offered by a career in endocrinology and diabetes to its trainees, which were also covered by a closing talk from Frank Waldron-Lynch (Cambridge).

SWEET SUCCESS

We are still in the process of analysing the formal feedback. However, we are delighted to say that the informal feedback has been extremely encouraging and that one-third of the delegates have already enquired about Society membership. (Hopefully some new members are reading this now!)

While our intention was to inspire our junior colleagues, the infectious enthusiasm left us, as a group of registrars, feeling motivated and recharged ourselves.

We thank the associated organisations for all their support: the Society for Endocrinology, Diabetes UK and the Association of British Clinical Diabetologists. We are grateful for the additional sponsorship secured by the YDEF team, without whom the event would've proved difficult to host. We look forward to ongoing support and collaboration, which we hope will allow for future successful events across the country.

Finally, particular mention must be made of Anna Mitchell (former Early Career Steering Group Chair, Society for Endocrinology), Muna Nwokolo (former YDEF Chair) and Amar Puttanna (YDEF Chair), who propelled this idea into motion. We'd also like to extend special thanks to all of our faculty (pictured, plus Ali Karamat (West Midlands) and Tahseen Chowdhury) who so generously gave up their Saturdays to inspire early career trainees – some of whom will be our future specialty colleagues.

If, after reading this, you yourself might consider running a Taster Day, please do get in touch (**louise.hunter@doctors.org.uk** or **shaziahussain@doctors.org.uk**).

LOUISE HUNTER & SHAZIA HUSSAIN
Clinical Committee SpR Representatives, Early Career Steering Group

REFERENCE

1. Puttanna *et al.* 2017 *Diabetic Medicine* **34** Suppl 1 P260 (doi:10.1111/dme.24_13304).

SUPPORTING PATIENTS:
BIRMINGHAM AND WEST MIDLANDS PITUITARY FOUNDATION

DAVID'S STORY

'I was diagnosed with my pituitary condition, empty sella syndrome, in late 2002. My consultant at that time recommended that I should join the Pituitary Foundation. However, due to various circumstances and the pressure of work commitments, I didn't join the group until 2012.

The Pituitary Foundation supports both patients and healthcare professionals in numerous ways. Over time, I have met many people with a similar condition to my own, or with more severe or varied diseases, but all of us have much in common. Being able to discuss our conditions, treatments or concerns with one another allows us not only to share our experiences, but also to offer support to one another if needed.

Since joining, I have attended many interesting, informative and helpful meetings, expanding my knowledge both of the pituitary and of a holistic approach. The speakers have included a range of healthcare professionals, who have all offered wide-ranging advice about the pituitary and related issues, as well as general health recommendations. Recent topics have included vitamin D and bone health, dynamic function tests and emergency hydrocortisone injection training. It is always helpful to have an update and practical session on the preparation and administration of this vital injection. We have also occasionally had speakers from the Pituitary Foundation itself.

'Since joining, I have attended many interesting, informative and helpful meetings, expanding my knowledge both of the pituitary and of a holistic approach.'

The sessions have all proved of value not only to patients but also to their carers, who are very welcome at the meetings. We are grateful to all those who give up their Saturday mornings to support us.

As well as the valuable opportunity to share experiences and suggestions with other members before and after the formal part of our meetings, most members also enjoy a social get-together for lunch at a local pub at least once a year. This gives us the chance to get to know one another better.'

DAVID LYNAM

Members benefit from friendly local meetings with healthcare professionals. ©L Shepherd

A SOURCE OF SUPPORT

The Pituitary Foundation not only raises awareness of pituitary conditions among patients, it also provides information and resources to healthcare professionals, who may not commonly deal with such diseases.

The Foundation achieves this by producing numerous free publications and promoting campaigns to improve detection, care and safety.

'We encourage all healthcare professionals to signpost patients to the Pituitary Foundation for help and support when diagnosed.'

These include the 'Know your insipidus from your mellitus' campaign, which was aimed at accident and emergency staff, nurses and pharmacists working in non-endocrine settings, and highlighted the importance of desmopressin as a life-saving medication for individuals with diabetes insipidus.

Our 'Get red flagged' campaign encouraged patients with adrenal insufficiency to register with their ambulance trust so their condition is flagged on the trust's system. The accompanying factsheet detailed how patients can register, so that if they ever call 999, the call will be flagged for priority attendance by a vehicle carrying emergency hydrocortisone.

This year, we ran a campaign to improve opticians' awareness of pituitary tumours, to reduce time to diagnosis. Information related to all campaigns, past and present, can be found at **www.pituitary.org.uk** or by email from **campaigns@pituitary.org.uk**.

We encourage all healthcare professionals to signpost patients to the Pituitary Foundation for help and support when diagnosed. As David says in his pituitary story here, new members and their carers are always welcome at meetings, and the Foundation is always willing to offer help and support.

MAKING CONTACT

www.pituitary.org.uk

www.facebook.com/pituitaryfoundation

www.twitter.com/pituitary_org

Patient support and information helpline
0117 370 1320 (Mon–Fri 10.00–16.00)
helpline@pituitary.org.uk

Endocrine nurse helpline
0117 370 1317 (Mon 10.00–13.00 and 18.00–21.00, Thu 09.00–13.00)

General enquiries (e.g. publications)
0117 370 1333
enquiries@pituitary.org.uk

The Society for Endocrinology is committed to supporting groups that represent patients with endocrine conditions by facilitating dialogue with the medical community. See **https://www.endocrinology.org/outreach/patient-support** for a list of groups supported by the Society.

SOCIETY GRANT SUPPORTS ENDOCRINE NURSES

The Society for Endocrinology is delighted to promote its exciting grant for its Nurse Members.

The new Endocrine Nurse Grant will support nurses who seek funding for a research or audit project to enhance nursing/clinical practice, or those who wish to produce preliminary data as part of a full application for a competitive doctoral research fellowship at the start of a PhD programme.

There will be two deadlines per year: 23 May and 28 November. The next is in May 2018. Up to £5,000 will be available at each deadline.

More details are available at **www.endocrinology.org/grants-and-awards**.

Developed by the Society's Nurse Committee, this grant will enhance the profile of those within the nursing profession, and will provide an additional member benefit by extending the Society's grants portfolio.

> *"The launch of this grant provides an excellent opportunity for nurses working in endocrinology to undertake a piece of research or audit. This will fundamentally not only improve practice and positively impact upon patient care, but enhance the nurses' professional profile."*
>
> ***Lisa Shepherd, Chair, Nurse Committee***

LISA SHEPHERD

NURSE COMMITTEE CHAIR

This issue of *The Endocrinologist* brings the exciting announcement of the winner of the second Endocrine Nurse Award. It gives me great pleasure to congratulate Janet Lewis. As we heard in issue 117 (Autumn 2015), Janet worked hard campaigning, in collaboration with patients with neuroendocrine tumours, for equitable care in Wales. The achievement of this award demonstrates the impact that collaborating with patient support groups can have. I look forward to hearing how Janet achieved this at the Endocrine Nurse Update 2018, on 16–17 April in Birmingham.

Our other article also demonstrates the importance of patient support groups, not just when a person is diagnosed, but also through the continuing support it can offer. I thank David Lynam for his article, which describes the benefits of joining a support group, as well as the importance of healthcare professionals signposting patients to support groups at diagnosis. Healthcare professionals have a reciprocal relationship with these networks, and much can be learnt from one another, as David explains.

I am proud to announce that, for the first time in the history of the Society for Endocrinology Nurse Committee, from January 2018 we will have representation from all countries of the UK: England, Northern Ireland, Scotland and Wales. This is a great opportunity to ensure that we reach out to all endocrine nurses in order to support and represent them.

Please continue to send us your comments and suggestions for content for *The Endocrinologist* and for nurse conference programmes, as well as anything else you would like to share. I thank all the endocrine nurses out there for their continued hard work and commitment to patients with endocrine disorders, and hope that you have time to enjoy the festive period.

BEST WISHES

LISA SHEPHERD

2018 ENDOCRINE NURSE AWARD WINNER

The Society is delighted to announce that the winner of the Endocrine Nurse Award for 2018 is Janet Lewis, Endocrine Nurse Specialist at the University Hospital of Wales, Cardiff. Janet was chosen for the award because of her leadership in devising recommendations that improve the healthcare provision and equality for patients with neuroendocrine tumours (NETs).

Janet said, 'We researched the Welsh Cancer Delivery Plan, amongst other documents. This stated that all patients with cancer should have equal access to treatment, regardless of where they lived in Wales, and access to a clinical nurse specialist, of which the NET patients had neither. The effect of these recommendations is that the standard of care that NET patients in Wales receive has improved and become equitable.'

IN THE JUDGES' WORDS...

'Janet has demonstrated the power of the Endocrine Specialist Nurse's voice in supporting patients with NETs. She has networked at a national level with local government and patient support groups, and helped lead change in the support and management of patients in Wales with NETs, with a significant increase in funding and specialist clinicians to provide a quality NET service.'

'Janet has helped transform a regional/Welsh service for the good of patients, engaging external commissioners and national authority. This is really transformational.'

Janet Lewis

The Society for Endocrinology's Endocrine Nurse Award recognises individuals who have demonstrated innovative and successful nurse-led initiatives in the endocrine field that have advanced best practice in research, education or patient care.

If you have a nurse colleague that you would like to nominate for the 2019 Endocrine Nurse Award, remember that applications are now open until 29 June 2018. See **www.endocrinology.org/grants-and-awards/prizes-and-awards/endocrine-nurse-award**.

Endocrine ACADEMY

www.endocrinology.org/events

SAVE THE DATE

Society for Endocrinology

Endocrine NURSE UPDATE

16–17 April 2018

Hilton Birmingham Metropole

NEC, BIRMINGHAM, UK

Aimed at both established and new-to-post nurses, the event focuses on best practice and the latest developments in the field. This is an annual two-day residential training event for specialist endocrine nurses featuring interactive sessions, combined lectures, workshops and networking opportunities.

managed by bioscientifica

Royal College of Nursing

RCN ACCREDITED

This programme has been accredited by the RCN Centre for Professional Accreditation until September 4th 2018. Accreditation applies only to the educational content of the programme and does not apply to any product.

Clinical Endocrinology Trust

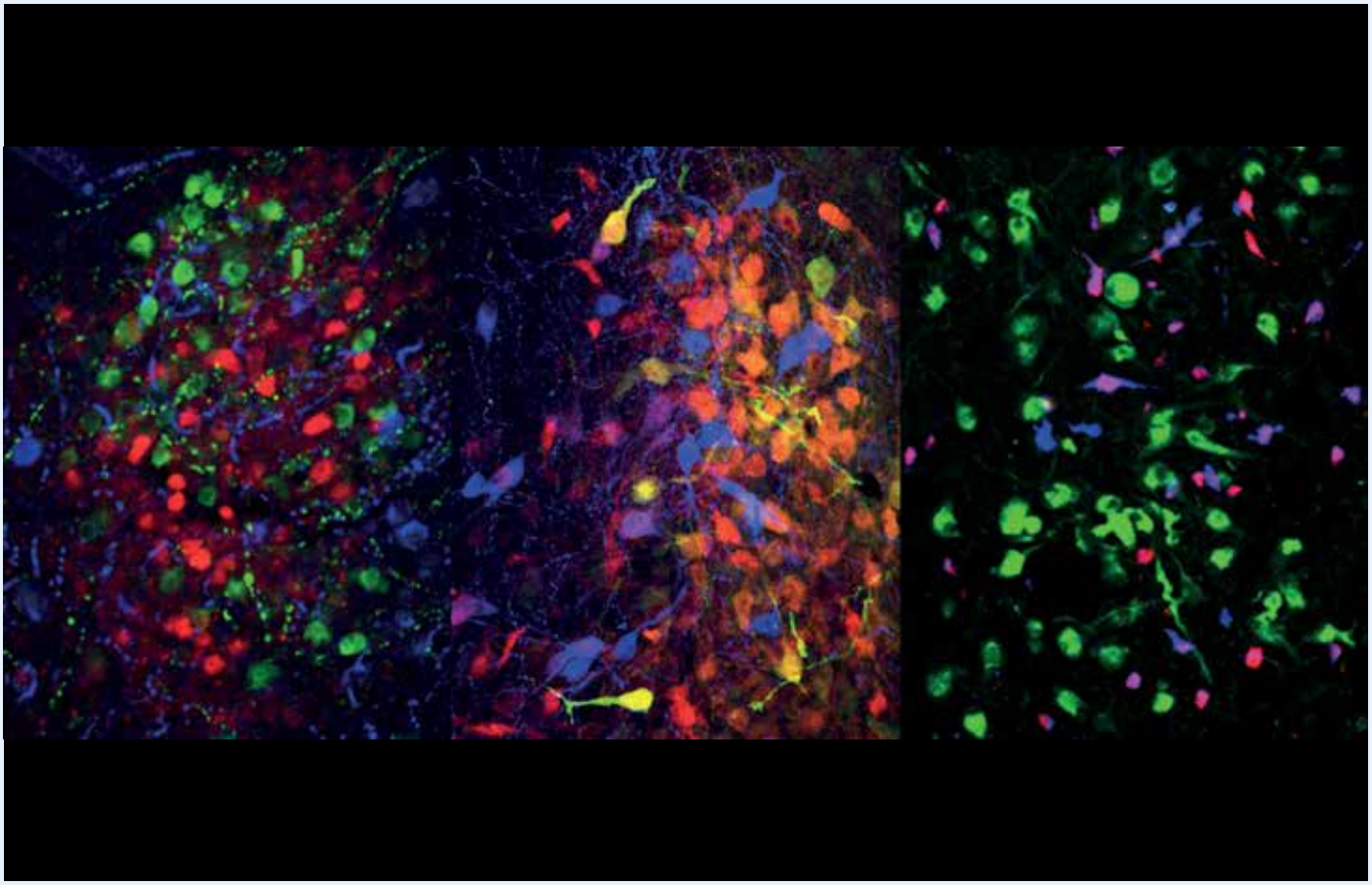
Images in ENDOCRINOLOGY

Here is the latest highlight from our journal Cover Art Competition, showcasing the best images in endocrinology.

COVER IMAGE FROM *JOURNAL OF ENDOCRINOLOGY*

DECEMBER 2017

The images depict some key molecular determinants of corticotrophin-releasing hormone (CRH) signalling in the hypothalamus of laboratory rodents and humans. In mice (left), secretagogin co-exists with neither oxytocin nor vasopressin. In contrast, a subset of vasopressin-positive and oxytocin-positive neurones can co-express secretagogin in rats (centre) and humans (right) (red, secretagogin; green, vasopressin; blue, oxytocin). From Romanov *et al.* 2017 *Journal of Endocrinology* **232** R161–R172. *Credit: RA Romanov, T Harkany (Medical University of Vienna, Austria), A Alpár (Semmelweis University, Budapest, Hungary), T Hökfelt (Karolinska Institutet, Sweden).*



Enter our Cover Art Competition

for *Journal of Endocrinology, Journal of Molecular Endocrinology* and *Endocrine-Related Cancer.*

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Not recommended in patients over 75 years of age. **Paediatric population:** Should not be used in children and adolescents below 18 years. **Method of administration:** Swallow tablets whole with water and preferably with food; do not cut, chew or crush. **Contraindications:** Hypersensitivity to active substance(s) or to any of the excipients. Uncontrolled hypertension. Current seizure disorder or a history of seizures. Known central nervous system tumour. Acute alcohol or benzodiazepine withdrawal. History of bipolar disorder. Any concomitant treatment containing bupropion or naltrexone. Current or previous diagnosis of bulimia or anorexia nervosa. Dependency on chronic opioids or opiate agonists (e.g. methadone), or acute opiate withdrawal. Concomitant administration of monoamine oxidase inhibitors (MAOI); at least 14 days should elapse between discontinuation of MAOI and initiation of treatment with Mysimba. Severe hepatic impairment. End stage renal failure or severe renal impairment. **Warnings and precautions (see SmPC for full details): Suicide and suicidal behaviour:** Closely supervise patients particularly those at high risk, especially in early treatment and following dose changes. **Seizures:** Bupropion is associated with a dose-related risk of seizures. Exercise caution when prescribing to patients with predisposing factors that may increase the risk of seizure. **Patients receiving opioid analgesics:** Do not administer to patients receiving chronic opiates. The attempt to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is very dangerous and may lead to a fatal overdose or life endangering opioid intoxication (e.g. respiratory arrest, circulatory collapse). **Allergic reactions:** Discontinue if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g. skin rash, pruritus, hives, chest pain, oedema, and shortness of breath) during treatment. **Elevation of blood pressure:** Use with caution in controlled hypertension and do not use in uncontrolled hypertension. **Cardiovascular disease:** Use with caution in active coronary artery disease (e.g. ongoing angina or recent history of myocardial infarction) or history of cerebrovascular disease. **Hepatotoxicity:** Mysimba is contraindicated in severe hepatic impairment and not recommended in mild or moderate hepatic impairment. Patients with suspected drug-induced liver injury should discontinue treatment. **Renal impairment:** Mysimba is contraindicated in end-stage renal failure or severe renal impairment, and is not recommended in moderate renal impairment. Dose reduction is not necessary in mild renal impairment. **Neuropsychiatric symptoms and activation of mania:** Use with caution in patients with a history of mania. **Lactose:** Do not use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. **Other:** The consumption of alcohol during Mysimba treatment should be minimised or avoided. **Effects on ability to drive and use machines:** It should be taken into account that dizziness may occur during treatment. **Undesirable effects:** Adverse reactions reported in subjects who received Mysimba, naltrexone alone or bupropion alone. **Very common (≥1/10):** Anxiety; insomnia; headache; restlessness; abdominal pain; nausea; constipation; vomiting; arthralgia; myalgia. **Common (≥1/100 to <1/10):** Lymphocyte count decreased; hypersensitivity reactions e.g. urticaria; decreased appetite; irritability; affective disorders; depression; dizziness; tremor; dysgeusia; disturbance in attention or concentration; lethargy; lacrimation increased; tinnitus; vertigo; palpitations, electrocardiogram change; hot flush; chest pain; dry mouth; toothache; diarrhoea; abdominal pain upper; hyperhidrosis; pruritus; alopecia; rash; sweating; ejaculation delayed; feeling jittery; energy increased; chills; fever. **FOR A FULL LIST OF ADVERSE EVENTS PLEASE CONSULT THE SUMMARY OF PRODUCT CHARACTERISTICS. NHS Price:** £73.00 per box of 112 tablets. **Legal Classification:** POM. **MA number:** EU/1/14/988/001. **Marketing Authorisation Holder:** Orexigen Therapeutics Ireland Limited, 2nd Floor, Palmerston House, Fenian Street, Dublin 2, Ireland. **Further information is available on request from:** Consilient Health (UK) Ltd, No.1 Church Road, Richmond upon Thames, Surrey. TW9 2QE or Mysimba@druginfo.com. **Job Code:** UK/MYS/0417/0066 **Date of preparation of PI:** April 2017

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Orexigen®: 0800-051-6402 or Mysimba@druginfo.com

References

1. Billes SK, Sinnayah P, Cowley MA. Pharmacol Res. 2014 Jun;**84**:1–11.
2. Greenway FL *et al.* Lancet 2010;**376**:595–605.
3. Apovian CM *et al.* Obesity 2013;**21**:935–943.
4. Hollander P *et al.* Diabetes Care 2013;**36**:4022–4029.
5. Wadden TA *et al.* Obesity 2011;**19**:110–120.
6. Mysimba SmPC 2017.

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